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ON THE CONDITIONS NECESSARY FOR THE CONTINUOUS GROWTH OF HYPOPHYSECTOMIZED ANIMALS*

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Hypophysectomized animals (dogs and rats) can be stimulated to undertake and continue a growth equal to or somewhat in excess of that normal for the species. We have hitherto produced these results with the use of relatively simple aqueous alkaline extracts† of the anterior hypophysis (1). The growth provoked in hypophysectomized rats was reported in 1933 (2). During a period of 120 days it was continuous and was approximately a gram daily. In the case of hypophysectomized puppies the continuous injection of the same crude extracts produced dogs of somewhat greater skeletal dimensions than their litter mate controls (2).

On the other hand, the protracted use of somewhat more purified growth hormone preparations from the anterior hypophysis has given results which differ in at least one important way from those just narrated. The more purified extracts, while giving an excellent initial growth response, sooner or later cease to evoke this response and, indeed, with continuous use of them, hypophysectomized animals enter upon a phase of growth stasis or actual decline in weight. The period of initial maximal response to purified growth extracts is usually 30 to 40 days in length and thus fortunately exceeds the time necessary for tests of potency of such extracts. The phenomenon of ultimate cessation of growth in the employment of such extracts has hence not interfered with purification procedures with the growth hormone. But an understanding of the phenomenon might contribute significantly to our further enlightenment as to the nature of the growth process itself, i.e., the conditions essential for growth. The

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†The aqueous alkaline extracts were made as follows: A given amount of frozen, ground beef hypophyses is taken up in 7½ volumes of 0.04 N $Ba(OH)_2$, extracted in the ice box 18 hours, then passed 4 times through a brine-cooled Sharples centrifuge. The supernatent is neutralized to pH 8.0 with 0.2 N H_2SO_4 and any excess barium precipitated out by the addition of a solution of Na_2SO_4. The solution is again centrifuged and the clear, cherry-red supernatent is ready for use.

The alkaline extract used in these experiments stimulated 50 gm. growth in adult female rats in the 20 days standardization period.

phenomenon, furthermore, has been used as one of the supports of the theory of anti-hormones recently elaborated by Collip and collaborators at Montreal (3). The ultimate cessation of growth in such animals has been looked upon by Collip as due to the operation of an anti-growth hormone. An entirely different interpretation of this phenomenon is suggested by the data herewith presented.

The rapid and continuous growth of hypophysectomized animals which may be provoked by the daily injection of relatively crude anterior hypophyseal extracts is shown in Figure 1. On the other hand, if a somewhat

FIGURE 1.

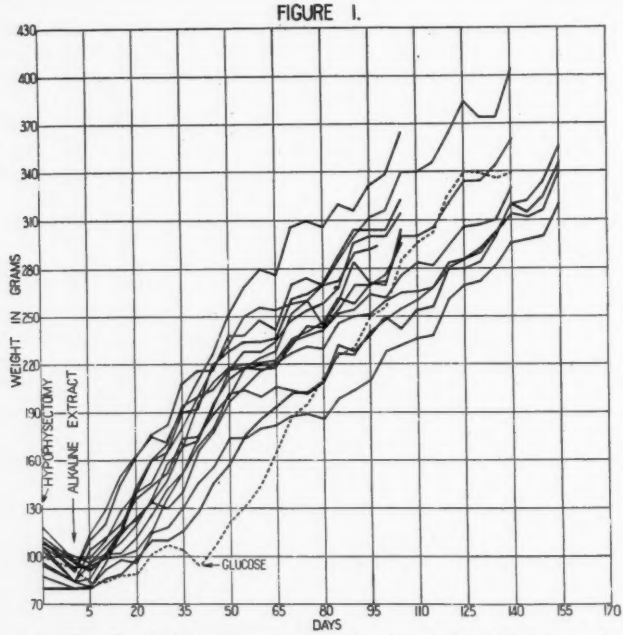

Figure 1. Growth of 14 hypophysectomized female rats injected daily with an alkaline extract of beef anterior hypophysis for a period varying from 100 to 155 days.

A single animal only—that represented by the dotted line—ceased growth after 30 days of treatment and thereafter rapidly declined. After a week of decline, daily intraperitoneal injection of glucose was begun and the daily injections of alkaline extract were continued.

more purified extract—one prepared by the use of flavianic acid (2) and briefly designated "the flavianate"‡—is employed, the phenomenon mentioned at the outset of this paper is shown in typical form (Figure 2). For the first 30 days the growth of these hypophysectomized rats was

‡The flavianate was made as follows: The standard alkaline extract is acidified and then precipitated in 90 per cent acetone. The precipitate is washed with 100 per cent acetone and anhydrous ether and is dried. An aqueous alkaline extract is made of this powder, and the insoluble material is discarded. The extract is brought to pH 6.5 and the precipitate which is formed is centrifuged off and discarded. The supernatent is then brought to pH 5.5 and 2 per cent flavianic acid is added to a concentration of 0.1 per cent. The precipitate which forms is centrifuged off, is washed with 95 per cent alcohol, 100 per cent alcohol and anhydrous ether, and dried in a desiccator at room temperature. This powder is dissolved in slightly alkalinized water, neutralized and injected.

The flavianate used in these experiments stimulated 48 gm. growth in adult female rats in the 20 day standardization period.

rapid, a gain of approximately 2 gm. daily resulting. Soon this growth practically ceased and, in spite of the continued injection of the "flavianate" for a total of 105 days, growth stasis and indeed a gradual decline in weight resulted. All but two animals of a group of eleven finally succumbed. These two were treated with a crude alkaline aqueous extract of the hypophysis, with the immediate resumption of rapid growth, as shown in Figure 2.

This experience was so striking that we determined to repeat the experiment at once, modifying it only to the extent of prompt intervention with the crude growth extract after the appearance of outspoken decline or cessation of growth. The experience with the two survivors of the pre-

FIGURE 2.

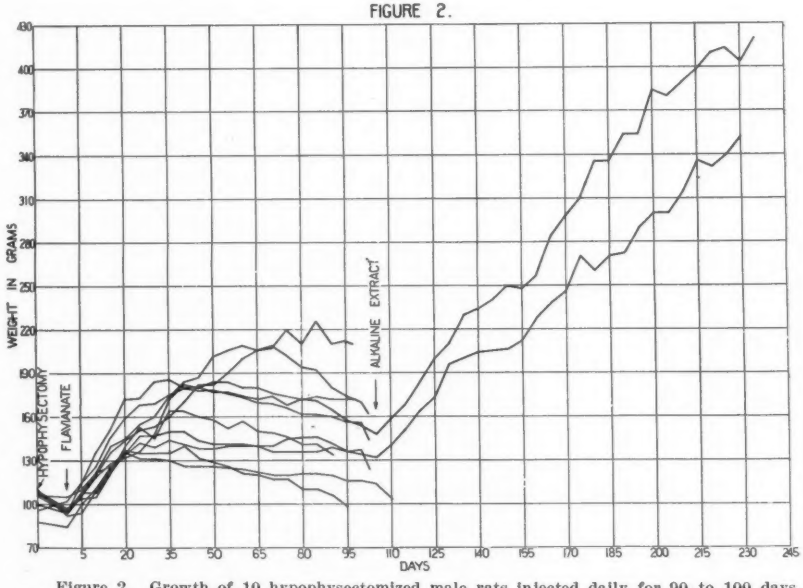

Figure 2. Growth of 10 hypophysectomized male rats injected daily for 90 to 100 days with flavianate prepared from beef anterior hypophysis. Eight of the 10 animals succumbed or were sacrificed after 105 days of treatment, but in the case of 2 of them, injection of the simpler alkaline extract was substituted for the flavianate.

ceding experiment was easily repeated with a group of four individuals, as shown in Figure 3.

The experiments enumerated would appear to have amply shown that: (1) The initial period of growth provoked in hypophysectomized animals by the use of partially purified growth hormone preparations is followed by cessation of growth; (2) such animals can be induced to resume rapid growth when given a less purified extract in their period of growth cessation or decline.

The hypothesis that an anti-growth hormone developed and that it caused the growth decline does not seem to be valid, for the growth decline

was spectacularly changed by the employment of cruder extracts of the anterior hypophysis. Both the somewhat purified and the cruder growth solutions at first provoked the same amount of growth in hypophysectomized test animals and the cruder extract could hence not be looked upon as working its effect by virtue of a higher content of the growth hormone—a content which could conceivably overbalance the anti-hormone that had arisen. It was consequently incumbent on us to seek another explanation for the continuous growth of hypophysectomized animals which crude extracts induce, and the conception nearest at hand is that other hormones are necessarily administered when the cruder extracts are employed. Attention must be called to the fact that the decline and ultimate failure of

FIGURE 3.

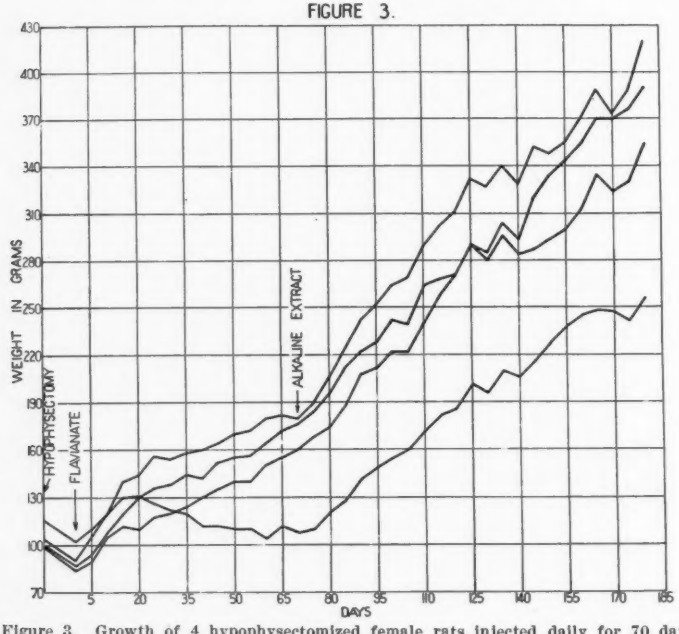

Figure 3. Growth of 4 hypophysectomized female rats injected daily for 70 days with flavianate and thereafter with alkaline extract.

growth in animals receiving growth hormone extracts has never been exhibited by normal animals but only by hypophysectomized ones, so that the Collip concept involves the readier elaboration of an anti-hormone by a defective animal (an hypophysectomized one) than by a normal one. Attention must also be called to the striking correspondence in the period in which growth decline was manifested with the period of the maximum mortality of young untreated hypophysectomized animals. During a period of several months, hypophysectomized animals were used extensively as test objects for various types of extracts prepared in this laboratory. Wherever possible, the animals selected for trial of extracts were

those in better condition, gradually leaving a very considerable group of hypophysectomized animals untreated. These "control" animals were maintained on the same diet and in the same heated cages used for those employed in experiments. The average survival time of 135 of these untreated female rats hypophysectomized at 40 to 60 days of age (128 to 146 gm. body weight) was 40 days†—a rather remarkable correspondence with the time at which growth declines when such animals are treated with purified growth extracts both in our own experiments and in those of Collip.

It must not be forgotten that hypophysectomized animals are deranged in several fundamental mechanisms—for instance, in their carbohydrate and fat metabolism—and that an increasing deficiency in one or more of these mechanisms may finally prohibit growth. A remarkable example of such a dependency has been furnished by the occasional failure of the growth of hypophysectomized animals even though they received the crude aqueous alkaline extract. In these instances, immediate daily intraperitoneal injection of glucose not only acts to save the life of such an animal but in the most striking way permits the growth hormone to now bring about immediate energetic growth. An animal was failing rapidly (Figure 1, dotted line); its fur was rough, it had diarrhoea, consumed little or no food and remained cold and in a humped posture in its cage. Death was expected daily, when, almost half-heartedly, intraperitoneal injections of glucose§ were commenced, once daily. A marked change occurred within 48 hours; within four or five days it was apparent from the animal's appearance and activity, its appetite and especially from its sharp gain in weight, that much more than a rescue from death had been effected. A simple explanation may be at hand for these spectacular effects; for besides the action of the glucose to raise the level of the blood sugar, there is brought about a sharp stimulus to appetite and food consumption which is markedly deficient in untreated hypophysectomized animals.

SUMMARY

1. Hypophysectomized rats (14 animals) were stimulated to continuous rapid growth by aqueous alkaline extracts of beef anterior hypophysis.

2. When a more purified extract was injected, an initial period of rapid growth lasting from 20 to 60 days was succeeded by growth decline and cessation, but the resumption of rapid continuous growth in such animals was stimulated by the secondary employment of aqueous alkaline extracts (17 animals).

3. Occasional failure with aqueous alkaline extract was spectacularly changed by the employment of parenteral glucose injections whereupon the extract invoked its customary pronounced stimulus to growth.

†With other diets the survival period is longer, but the comparisons made in the text are valid since these groups received the same diet.

§The animal received 0.25 cc. daily of a 20 per cent glucose solution for a two-weeks period. The dose was then increased to 0.5 cc. and was continued on that level for the duration of the experiment.

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PAGET'S DISEASE (OSTEITIS DEFORMANS)

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The well-known association between phosphorus, carbohydrate metabolism and bone development led us to study a series of cases of Paget's disease. This series of cases, though small, shows certain significant facts which it is hoped will stimulate others to study their cases along similar lines.

Hunter (1) says that "phosphorus compounds take part in at least four important metabolic processes. They are in some way essential to the storage or utilization of carbohydrate, they enter into the chemical changes which precede the contraction of muscle, they are concerned with the acid-base equilibrium and they are essential to the deposition of bone."

It has been known for some time that phosphorus is related to both carbohydrate metabolism and bone formation. In osseous dystrophies such as Paget's disease it should be possible to demonstrate certain characteristics pointing to involvement of carbohydrate and phosphorus metabolism. We were particularly interested from the standpoint of constitutional inheritance showing a disturbance in carbohydrate metabolism and bone formation. On the following page is a table giving the salient points.

An analysis of this clinical data shows that of twelve patients with Paget's disease, five, or 41 plus per cent, give a family history of diabetes mellitus. In two patients (Nos. 8 and 9) there was more than one member of the family afflicted with diabetes. In patient 8 both parents died of diabetes and one brother, still living, has diabetes.* A sister had had a parathyroidectomy for generalized osteoporosis. The patient had a giant cell sarcoma of the antrum, beginning, no doubt, in the ethmoid, removed twelve years previously. Patient 9 had two brothers and two sisters who died of diabetes; the latter also had goiters.

In regard to heights, it will be seen that twelve, or 100 per cent, had at least one member of the family 70 inches or more in height. In eleven families one or more members was 71 inches in height. In eight families one or more members was 72 inches in height. In patient 1 all members, both male and female (total four), were 71 inches in height.

In five families in which the weight was obtained one or more members weighed 200 pounds or more.

Two of the twelve patients, or 16 plus per cent, had uterine leiomyomata. Interestingly enough, one of us (R. C. M.) has a series of one hundred patients with uterine leiomyomata in which the incidence of familial

*We have since learned that this brother also has Paget's disease.

TABLE I

Patient No.	Age	Sex	Height	Family Heights	Family History	Remarks
1 F.S.	Years 42	♀	69 ins. (Was 72)	Father 71 ins. Mother 71 ins. Brother 71 ins. Sister 71 ins. (200 lbs.)	Father living. Mother living, heart dis. Brother has migraine.	Deafness, loss of height. Parathyroidectomy. 2 parathyroids removed. Had carcinoma of uterus. Hysterectomy 2 yrs. ago.
2 S.S.	67	♀	66 ins.	Father 71 ins. 2 Brothers over 72 ins.	Father dead, cause ? Mother dead, cause ?	Had a calcified fibroid. Arthritis all her life. Arteriosclerosis, generalized. Deafness. Glucose tolerance .087, .102, .125, .125.
3 V.T.	53	♂	68 ins. (Was 71) Weight 206 lbs.	Father 68 ins. (160 lbs.) Mother 69 ins. (over 200 lbs.) 1 Brother 71 ins. (245 lbs.)	Mother died of diabetes mellitus Father dead, cause unknown.	Deafness. Enlarged heart. Casts in urine. 2 parathyroids removed. Blood sugar 133 mgs.
4 S.E.	56	♂	72½ ins. (190 lbs.)	Father 72 ins. (210 lbs.)	Father died of cardio-renal disease. Mother died of Bright's disease. 1 sister dead, carcinoma of uterus.	Hyaline casts.
5 R.B.	64	♂	70 ins. (180 lbs.)	Father 71 ins. 1 Brother 71 ins. 1 Brother 70 ins.	Father dead, diabetes mellitus. Mother dead, coronary thrombosis.	Patient very fond of sweets.
6 T.T.	59	♀	66 ins. (165 lbs.)	Father 70 ins. Mother, not known Brother	Father dead, diabetes mellitus. Mother dead, "fractured hip".	Had cyst of radius operated upon, 1932. Blood pressure 210/80. 2 parathyroids removed with a thyroid adenoma.
7 F.M.	50	♂	71½ ins. Now 70 Weight 175 lbs.	Father 72 ins. Mother ?	Father dead, pulmonary tuberculosis Mother dead, cancer of uterus.	Fracture of clavicle. 2 parathyroids removed with thyroid adenoma.
8 M.M.	51	♀	64 ins. (140 lbs.)	Father 72 ins. (240 lbs.) Mother ? Brother 71 ins.	Father dead, diabetes mellitus. Mother dead, diabetes mellitus. Brother living, has diabetes. Sister had two parathyroids removed for osteoporosis.	Had a giant cell sarcoma removed from antrum, left side, in 1922. Recurrence at present in anterior part of upper jaw.
9 T.K.	63	♀	63 ins.	Father 72 ins. Mother ? 2 Brothers 72 ins.	Father killed, accident Mother died at 81 yrs. ? 2 brothers died of diabetes mellitus. 2 sisters have goiters and diabetes.	Generalized arteriosclerosis. Calcification of aorta. Angina pectoris. Bilateral oophorectomy 30 years ago.
10 G.L.	34	♀	66 ins. (134 lbs.)	Father 64½ ins. (140 lbs.) Mother 61 ins. (145-150 lbs.) Oldest Brother 72 ins. (200 lbs.) 1 Brother 70 ins. (155 lbs.) 1 Brother 65 ins. (145 lbs.) 1 Brother 70½ ins. (160 lbs.) 1 Brother 70½ ins. (155 lbs.)	Father died of pulmonary tuberculosis. Mother and brothers living. No diabetes or goiter.	Onset after pregnancy 2½ years ago.
11 S.D.	55	♀	65 ins. (190 lbs.)	Father 72 ins. 1 Brother 60 ins. 1 Brother 66 ins.	Father dead, age 94 yrs., senility. Mother dead, had goiter and liver trouble. 1 sister dead, carcinoma of stomach. 1 brother dead of tuberculosis.	Fibroid. Enlarged sella. Goiter. Deafness.
12 A.P.	51	♂	73 ins.	Father 73 ins. Mother 69 ins. 7 Brothers, all over 72 ins. 2 Sisters 69 ins.	Father dead, pneumonia Mother dead, pneumonia 1 brother, pneumonia. 1 sister, pneumonia.	

tallness is unusually high. Also it is well known that leiomyomata and diabetes are frequently associated.

While our series is small, nevertheless, if a like ratio of familial diabetes, height and obesity is found to be generally true, then these facts become of etiological significance. The two outstanding constitutional features are the family history of diabetes mellitus and comparative tallness.

This gives us an opportunity to correlate certain data as a means to etiological approach. In Paget's disease serum phosphatase is increased from ten to fifty times the normal (Bodansky and Jaffe, 2; Kay, 3a, and others). In our series this was also found to be true. Our average for the series was 19.56 units. Bodansky and Jaffe (2) call attention to the familial factor in Paget's disease and state that the determination of serum phosphatase might offer a means of searching for the earliest evidence of Paget's disease within families in which the disease has been found in one or more of the members. We might add the suggestion that one should also be watchful for osseous dystrophies in families with diabetes and tallness. We made glucose tolerance studies on five of our patients and are completing this procedure on the remaining seven. We find that their response is not unlike that of the true diabetic.

In view of this finding we have started this group on a definite weighed diet consisting of carbohydrate 150 grams, fat 110 grams, protein 70 grams, and using insulin, units XV, t.i.d., a.c* The rapid clinical response (occurring almost immediately—seven days), characterized by the disappearance of so-called bone and head pains, with increased strength, was remarkable. (These were ambulatory patients.) Cooperation has been excellent in this group. That this was not a purely psychic effect is apparent from the concomitant drop in blood phosphatase as determined by repeated blood analyses in all five cases. This drop in one case was phenomenal, from a consistently high level varying between 29 and 41.4 Bodansky units to 2.8 Bodansky units in ten days—and remaining at this low level.

Since there is new bone formation in Paget's disease, it is not surprising that serum phosphatase is increased. We can readily understand, therefore, with the phosphatase increase, that carbohydrate disturbances should be found.

One other fact may be mentioned here and that is the frequent finding of arteriosclerosis. Of course, the disease occurs at an age when arteriosclerosis is usually found, but this almost uniform feature is seemingly more frequent in this disease than in other diseases of this age group. The association of diabetes mellitus and arteriosclerosis (4) is so well-known that mention is only made of it. Suffice it to say that the pituitary plays a definite, if not leading, rôle in both carbohydrate metabolism and the production of arteriosclerosis.

*Since this was written we have given 175-200 grams of carbohydrate and only 50 grams of fat.

Roberts and Cohen (5), Knaggs (6), Locke (7), Kay and associates (3b) are all of the opinion that atheromatous arteries are a general accompaniment of Paget's disease. In Kay and associates (3b) thirty-four cases, nineteen showed severe arteriosclerosis, six moderate and four slight. In four there was no clinical evidence of arterial degeneration.

Cone (8) believes from his autopsy material that Paget's is the result of chronic cardiovascular disease. He says, "It is the outcome of long continued, intermittent high and low pressure, coupled with changes in organs of internal secretion so commonly accompanying cardiovascular disease. The bone changes are more severe where the pituitary, thyroid or parathyroid glands are independently diseased."

Kay found the plasma phosphatase slightly above normal in uncomplicated diabetes mellitus. In Paget's disease he also found a great increase over normal blood phosphatase. In two cases of acromegaly, one with glycosuria, Kay found the figures as 0.22 and 0.32, being, therefore, above normal average (0.15) (Kay's method). In a case of hyperpituitary gigantism the figure was 0.38, also above the normal.

Bodansky (9) found that carbohydrate ingestion raised serum phosphatase, that protein lowered it and that fat was apparently without effect. He says that the increased serum phosphotase after carbohydrate ingestion is probably to be explained by increased functional activity of the organs and tissues involved in the processes that follow ingestion. Robison (10) ascribes a digestive function to the intestinal phosphatase.

In our series of patients with their familial diabetes, tallness and obesity, a constitutional predisposition is no doubt shown by these characteristics. Can these features be explained on one basis and can this osseous dystrophy of Paget's disease also find an explanation in this same basis? Experience teaches us that it is both logical and best to place the etiology of disease on one basis. We would like to advance the opinion that involvement of the pituitary gland could explain the diabetes, familial tallness and osseous dystrophy of Paget's disease.

Today carbohydrate metabolism cannot be regarded as influenced solely by the pancreas. The brilliant work of Houssay (11a) and his associates has given the pituitary a leading rôle in carbohydrate metabolism. These workers have shown that pancreatectomy performed on tadpoles and dogs results in severe diabetes mellitus. Following the pancreatectomy hypophysectomy is performed with resultant disappearance or modification of the diabetes. Re-implantation of the pituitary re-establishes the severe diabetes. Dogs so operated upon live for years.

Injection of anterior lobe extracts into these animals results in marked glycosuria (11b). It is also known that posterior lobe extract causes a slight rise in blood sugar and this extract overcomes the convulsions produced by insulin hypoglycemia. The simultaneous injection of insulin and posterior lobe extract results in no fall in blood sugar; in other words, these extracts are antagonistic in pharmacologic action.

Hypophysectomy in dogs not infrequently results in a fatal hypoglycemia and these animals so operated upon are unusually sensitive to insulin; very small doses of this extract result in a marked hypoglycemia. Pituitary cachexia or Simmond's disease is characterized by severe hypoglycemia and individuals suffering from this disease are very sensitive to insulin.

In acromegaly (pituitary eosinophilism) diabetes mellitus is found in about forty per cent of individuals so affected.

In pituitary basophilism (Cushing's syndrome) hyperglycemia is frequently present. Contrariwise chromophobe adenomas and hypopituitarism in general are usually accompanied by an increased carbohydrate tolerance. It is also of interest that in both acromegaly and pituitary basophilism kyphosis is found.

While changes in the pituitary are not infrequently found in diabetes mellitus (Kraus, 12; Berblinger, 13), nevertheless they are no more characteristic of this disease than are the findings in the pancreas as demonstrated by Warren (14). Cushing (15) found that subtotal pancreatectomy in dogs increased the secretion of the posterior lobe. Dogs with pituitary insufficiency withstand the extirpation of the pancreas better than normal dogs.

Joslin (16) has shown that diabetic children are overgrown. White (17) of Joslin's clinic found these children were 2.7 inches above normal height. Joslin was of the opinion that this was due to a pituitary element.

The familial tallness found in Paget's disease and pituitary association is a most logical one. The relationship between the pituitary and osseous development is amply shown by clinical data. Acromegaly, gigantism, pituitary dwarfism are well-known examples of pituitary and bone relationships.

That the parathyroids do not play a major rôle in this disease is shown by the uniformly normal blood calcium figures. In our series the urinary calcium determination seemed to point to a rather definite calcium retention. Four patients in our present series were subjected to parathyroidectomy by Dr. Ballin without any apparent modification or regressioin of the disease process as determined by blood analysis or careful and frequent subsequent check-up.

That the parathyroid function may be influenced by pituitary activity is shown by the experiments of Hertz and Kranes (18) and by Anselmino and Hoffmann (19). Both workers showed that anterior lobe extracts produced hyperplasia of the parathyroids and, in addition, Anselmino and Hoffmann showed that these extracts raised the blood calcium level, which, however, was not the case when the parathyroids had been removed. They concluded, therefore, that in pituitary disturbances with calcium abnormalities the parathyroids were secondarily influenced by the state of the pituitary.

Hamann (20), in 1920, was of the opinion that Paget's disease is the result of a hypopituitary condition. This opinion, in view of more recent developments, is absolutely contrary to the known facts. For instance, hypopituitarism is associated with osseous underdevelopment and an increased carbohydrate tolerance.

Only one of our patients (No. 11) showed a large sella turcica, but, as is well known, the absence of roentgenologic evidence of pituitary hypertrophy is not deemed significant. We advised a series of deep x-ray treatments of the pituitary in this patient. She had a very marked generalized pigmentation of the skin, which cleared up under this form of treatment, but it is too early to say what effect, if any, this treatment will have on the progress of the Paget's disease.

If constant and characteristic findings were to be found in the pituitary in Paget's disease, the matter of etiology would be comparatively easy of solution. As we know, however, this is not the case and we must call upon our physiological knowledge to assist us in understanding the disease. The physiological chemists will, no doubt, contribute much to the solution of this and allied problems.

We, in conjunction with Dr. Lawrence Reynolds, have carried out a series of experiments for several months on dogs, using large doses of parathyroid extract (over 12,000 Hanson units) and growth hormone (The Wilson Laboratories) in an attempt to produce osseous changes. We will report our findings later.

SUMMARY

We have observed that in twelve cases of Paget's disease herein reported five (41 per cent) gave a family history of diabetes mellitus. In two cases (16 per cent) more than one member of the family had diabetes, and in one of these both parents died of diabetes, and a brother, still living, is so afflicted.* It was noted that a sister in this family had had a parathyroidectomy for generalized osteoporosis.

Five of our twelve patients have shown a response to the glucose tolerance test not unlike that of a diabetic and are now under treatment such as would be appropriate for a response of such a nature, that is, a weighed, constant diet covered adequately with insulin. Their clinical response has been very satisfactory.

As for height, twelve (100 per cent) had at least one member of the family 70 inches or more in height. In eleven families (92 per cent) one or more members was 71 inches in height. In eight families (66 per cent) one or more members was 72 inches in height.

As to weight, only five patients gave information, but all of these were of families in which one or more members exceeded 200 pounds.

*Also has Paget's disease.

In the light of the frequency of leiomyomata with familial tallness and leiomyomata with diabetes, it is interesting to note that two of our subjects of Paget's disease (16 per cent) had leiomyomata.

CONCLUSIONS

The observations reported suggest: (a) That constitutional inheritance plays a major rôle in the etiological development of Paget's osteitis deformans.

(b) The high incidence of familial tallness, diabetes mellitus and obesity are of great significance in pointing to these constitutional factors as providing the etiological background for the development of the disease.

(c) The suggestion is made that the pituitary gland function is primarily involved in the production of the disease process and that the parathyroid function is secondarily involved.

(d) From a practical therapeutic standpoint the first consideration would be one of constitutional prophylaxis, that is, a eugenic one in that the tall, obese individuals, especially those with a familial diabetic history, should not intermarry.

(e) In view of the fact that there is a familial diabetic history and the patients have a low carbohydrate tolerance, victims of Paget's disease should be treated as diabetics with weighed diet and insulin.

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THE SILHOUETTE METHOD FOR COMPARING THE VOLUMES OF THE TWO PARTS OF THE ADRENAL GLANDS IN SMALL ANIMALS

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The adrenal gland consists of two parts, each of which has a different structure and produces a different endocrine secretion. In addition to knowing the chemical changes and histological alterations which take place in the gland, it is also frequently desirable to learn of the variations in the amounts of the two kinds of tissue which compose it. The method described below makes possible a rapid estimate of the volumes of the two parts of the gland and still leaves the material available for sectioning and staining.

HISTORICAL

The classical method of finding the volume of objects of microscopic size is to measure the areas of the organ in serial sections of known thickness and magnification, and either calculate the size from these data or reconstruct the organ in an enlarged form. This is the reconstruction method. In the case of the adrenal, where the medulla is enclosed in the cortex like a peach stone in a peach, the volumes of the two parts have been estimated from the areas of the largest cross sections. The relative value of these methods was discussed in a recent paper by Carlson (1).

In 1922, Wislocki (2) published a method for examining material for the presence of adrenin-secreting tissue. As discovered by Henle (3) in 1865 and others, such tissue takes a characteristic stain with the salts of chromic acid and is, therefore, frequently referred to as chromaffin tissue. In 1911 and subsequently, Spalteholtz (4) described his method of making whole objects transparent by dehydration, bleaching and clearing in oil of correct refractive index.

Wislocki combined and modified these two methods to obtain cleared specimens in which the chromaffin tissue retained its chromic acid coloring while the rest of the preparation was transparent. This technic has been further modified as described below, so as to bring out the two different types of tissue in the adrenal glands of such small animals as rats and mice, and to permit their measurement.

DIRECTIONS

The glands are removed from the freshly killed animal, washed in normal salt solution to remove external blood, and freed from fat. When this has been done, they may be weighed in small, well-stoppered weighing vials. They are then prepared for projection as follows:

1. Freshly mixed fixing fluid for 3 hours.
   - 10% potassium dichromate ..... 30 cc.
   - 10% formalin ..... 10 cc.
   - Distilled water ..... 60 cc.
2. Rinse in tap water to remove fixing fluid.
3. 10% formalin (3 changes) for 3 days.
4. 70% alcohol (3 changes) for 3 days.
5. Bleaching solution.
   - Hydrogen peroxide ..... 25 cc.
   - 95% alcohol ..... 75 cc.
6. Bleach 2 hours in front of an electric light.
7. 95% alcohol (2 changes) 2 hours.
8. Absolute alcohol to dehydration.
9. Clearing solution (2 changes)
   - Benzyl benzoate ..... 1 part
   - Methyl salicylate ..... 2 parts

The glands are now ready for projection and tracing.

DISCUSSION

It should be noted that the technic so far given with the exception of the substitution of electric light for sunlight is essentially that described by Wislocki, as already noted.

The times indicated above are for rat adrenals which measure from 2 to 4 mm. in their greatest dimension. With such glands, about 10 cc. of fluid for a pair is used in each step except the bleaching where the quantity of fluid should be doubled.

Glands from freshly killed animals yield the best results. In rats kept at room temperature, adrenals removed 5 hours after death cleared satisfactorily and showed the chromaffin reaction of the medulla. The same was true of adrenals from rats placed in the ice-box immediately after death and kept for 16 hours before autopsy. Even after 36 hours, glands from rats kept in the ice-box gave enough of a chromaffin reaction to make the adrenals usable.

In removing the fat from the adrenals, care must be taken not to bruise or cut the gland. If this occurs, bubbles form beneath the capsule or in the gland tissue during the bleaching process. Such glands should be discarded, as they are distorted and useless either for the silhouette or the reconstruction methods. A loupe is a great aid in avoiding damage in cleaning the smaller sized glands.

The fixing fluid is unstable once it is mixed and becomes cloudy on standing more than a few days. The 10 per cent dichromate, however, can be kept indefinitely as a stock solution. The solution must not be allowed to act for more than 3 hours, otherwise reactions may occur which prevent the gland clearing properly. For the same reason, all traces of the fixing solution should be removed first by the rinse in water and then by changing the 10 per cent formalin as often as is necessary. Usually three changes will suffice.

The minimum period of 3 days in the formalin and the alcohols is purely empirical to keep the results comparable. In that time, each of these solutions should have its maximum effect. The minimum time that can be used still remains to be investigated. The glands can be stored in

70 per cent alcohol for periods up to at least 3 months without apparent damage.

The bleaching solution must be made up immediately before use. The rapid deterioration and initial variability of commercial peroxide solutions make the bleaching solution difficult to standardize. In this laboratory we have found it simplest to buy the 4 per cent peroxide solution of some reliable firm in 4-ounce bottles as needed and discard what remains unused after about two weeks.

The actual bleaching is done by placing the vial containing the gland on the turntable of an electric phonograph and concentrating on it by means of a bull's eye lens the light from a 250-watt electric bulb. This substitutes artificial light for sunlight but gets away from the variations in quality and quantity of the latter. The value of a sun lamp in this connection has not yet been tested (5). Heat-absorbing glass may be used to reduce the heating of the bleaching solution. It was not found necessary, however. To permit escape of gas and, at the same time reduce evaporation of the solution, a grooved cork is used in the bleaching vial. After bleaching, the gland should appear a dull white.

The clearing solution is made from benzyl benzoate and artificial oil of wintergreen. It has a refractive index of about 1.5440 at room temperature. The exact refractive index of the fluid is not a serious matter. This can be tested by running a small needle or other instrument with a fixed diameter through the center of a cleared gland and measuring the apparent diameter of it inside and outside the gland. It was thought for a time that the large size of the medulla, when measured by the silhouette method (see below), might be due to a magnifying effect on it of the convex transparent cortex. In fluids with refractive indices from 1.533 to 1.565, no such effect is measurable as shown by the needle test. The magnifying influence of the cortex on the medulla can, therefore, be disregarded.

After the gland is placed in the clearing oils a slow discoloration of the cortex takes place. If left in the oils for a month, the cortex becomes distinctly brownish. Glands stored in the clearing solution can be used up to four years and possibly longer after their initial clearing but they have the disadvantage of being opaque enough to dim the outline of the medulla and make it somewhat difficult to follow. During the first week in the solution, the cortex is clear; lets through the maximum amount of light and, therefore, glands should be traced at this time to yield the best results.

The tracing of the glands to get the silhouette of the cortex and medulla is done in a projection apparatus, the essential features of which are shown in Figure 1. An arc is used as the source of light. This reaches the gland after passing through the collimator lens which renders the rays parallel. The gland is held immersed in the clearing mixture of oils in a dish with a plane glass bottom. The objective lens is fixed so that the magnification remains the same and focussing is done by raising or lowering the stage on which the dish containing the object rests. A magnifica-

tion of between fifteen and twenty diameters has been found most convenient.

The apparatus for holding the gland consists of a pair of jaws and an arm rotating about an axis so that two views of the gland at right angles to one another can be presented before the lens in succession. The jaws are made from a small draughtsman's compass into which two needles with curved points have been fitted. The curved portion of the needle must be long enough so that the place where the needle enters the liquid is out of the visual field. The needle produces a slight meniscus at this

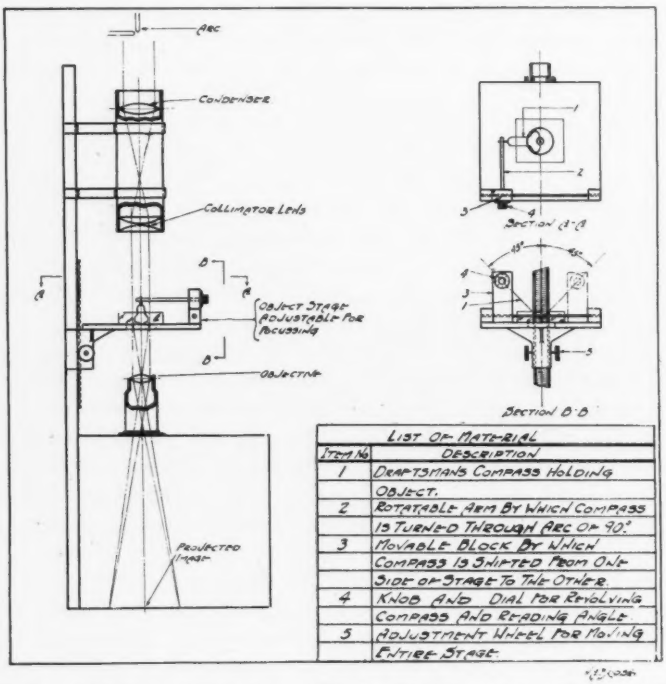
ARC
CONDENSER
COLLIMATOR LENS
OBJECT STAGE ADJUSTABLE FOR FOCUSSING
OBJECTIVE
PROJECTED IMAGE
SECTION A-B
SECTION B-B
LIST OF MATERIAL
ITEM No | DESCRIPTION
1 DRAFTSMAN'S COMPASS HOLDING OBJECT.
2 ROTATABLE ARM BY WHICH COMPASS IS TURNED THROUGH ARC OF 90°
3 MOVABLE BLOCK BY WHICH COMPASS IS SHIFTED FROM ONE SIDE OF STAGE TO THE OTHER.
4 KNOB AND DIAL FOR REVOLVING COMPASS AND READING ANGLE
5 ADJUSTMENT WHEEL FOR MOVING ENTIRE STAGE.

Figure 1. Projection apparatus for use with the silhouette method. (Diagrammatic.)

point which will distort the gland if it overlaps its outline. The image of the gland is projected on a plane surface beneath the lens.

To make the necessary tracings, the gland is placed in the holder immersed in the fluid and the image focussed on the drawing surface. The gland in one position, for example, X, figure 2, is projected and the outlines of cortex and medulla traced on card-board. Then, the holder is rotated and outlines of the view Y at right angles to X are likewise traced. The tracings are made on cold pressed drawing paper about 300 micra in thickness. This is a standard weight for drawing papers in sheets 19x24 inches. Scammon and Scott (6) pointed out the value of the uniform

thickness of Kodaloid, a commercial product for such work. Eighteen glands were traced on both Kodaloid and card-board. When the results derived from the two were compared, there was agreement to within 0.05 per cent. Kodaloid seems, therefore, an unnecessary refinement for this method.

The silhouettes of the medulla and of the cortex as outlined are cut out of the drawing paper with a sharp scissors. The blades must be held at right angles to the paper, so as to make a vertical and not a slanting cut. The areas thus cut out are weighed. The weight of the silhouettes of the cortex and the medulla are combined to get the weight of the entire gland.

The method of measuring areas of this size by weighing was found to be more rapid and as accurate as measuring the areas directly with a

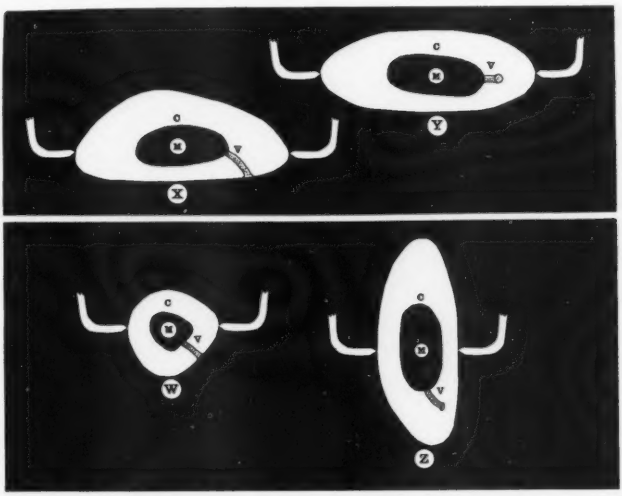

Figure 2. Diagrammatic views of adrenal glands as seen in the silhouette method. C-Cortex. M-Medulla. V-Central vein used to indicate the rotation of the gland in the apparatus.

planimeter (6). In twelve glands, the difference between the results of the two methods was less than 1 per cent.

For reasons to be explained later, we now take the 3/2 power of the weight of the silhouette of the whole gland and of that of the medulla. The derived value for the medulla is then expressed as a percentage of the derived value for the whole gland. This is done separately for the views X and Y in Figure 2. The two percentages are averaged and the result is the relative amount of medulla in the entire gland.

The 3/2 power may be calculated or read off from a table such as that of Huntington (7, p. 22). If extensive work is to be done, a table (Fig. 3) showing the relations between the ratio of two areas and their 3/2 powers may be constructed. With such a table available, all that is needed is to

Ratio	Volume %	Ratio	Volume %	Ratio	Volume %	Ratio	Volume %	Ratio	Volume %	Ratio	Volume %
1.00	100.0	2.00	35.3	3.00	19.2	4.00	12.5	6.00	6.8	9.00	3.7
.02	97.0	.02	34.8	.02	19.0	.05	12.3	.05	6.7	.10	3.6
.04	94.2	.04	34.3	.04	18.9	.10	12.0	.10	6.6	.20	3.6
.06	91.5	.06	33.8	.06	18.7	.15	11.8	.15	6.5	.30	3.5
.08	89.1	.08	33.3	.08	18.5	.20	11.6	.20	6.5	.40	3.5
1.10	86.7	2.10	32.8	3.10	18.3	4.25	11.4	6.25	6.4	9.50	3.4
.12	84.3	.12	32.3	.12	18.1	.30	11.2	.30	6.3	.60	3.4
.14	82.1	.14	31.9	.14	18.0	.35	11.0	.35	6.2	.70	3.3
.16	80.0	.16	31.5	.16	17.8	.40	10.8	.40	6.2	.80	3.3
.18	78.0	.18	31.0	.18	17.6	.45	10.6	.45	6.1	.90	3.2
1.20	76.0	2.20	30.6	3.20	17.5	4.50	10.5	6.50	6.0		
.22	74.1	.22	30.2	.22	17.3	.55	10.3	.55	6.0		
.24	72.3	.24	29.8	.24	17.2	.60	10.1	.60	5.9		
.26	70.6	.26	29.4	.26	17.0	.65	10.0	.65	5.8		
.28	69.0	.28	29.0	.28	16.8	.70	9.8	.70	5.7		
1.30	67.4	2.30	28.6	3.30	16.7	4.75	9.7	6.75	5.7	10.00	3.2
.32	65.9	.32	28.2	.32	16.5	.80	9.5	.80	5.6	.10	3.1
.34	64.4	.34	27.9	.34	16.4	.85	9.4	.85	5.6	.20	3.1
.36	63.0	.36	27.5	.36	16.2	.90	9.2	.90	5.4	.30	3.0
.38	61.7	.38	27.2	.38	16.1	.95	9.1	.95	5.4	.40	3.0
1.40	60.3	2.40	26.9	3.40	15.9					10.50	2.9
.42	59.0	.42	26.6	.42	15.7					.60	2.9
.44	57.8	.44	26.3	.44	15.6					.70	2.9
.46	56.6	.46	26.0	.46	15.5					.80	2.8
.48	55.5	.48	25.6	.48	15.4					.90	2.8
1.50	54.4	2.50	25.3	3.50	15.3			7.00	5.4	11.00	2.7
.52	53.3	.52	25.0	.52	15.1			.10	5.3	11.50	2.6
.54	52.3	.54	24.7	.54	15.0			.20	5.2		
.56	51.3	.56	24.4	.56	14.9			.30	5.1	12.00	2.4
.58	50.3	.58	24.1	.58	14.7			.40	5.0	12.50	2.3
1.60	49.3	2.60	23.8	3.60	14.6	5.00	8.9	7.50	4.9	13.00	2.1
.62	48.4	.62	23.5	.62	14.5	.05	8.8	.60	4.8	13.50	2.0
.64	47.5	.64	23.3	.64	14.4	.10	8.7	.70	4.7		
.66	46.7	.66	23.0	.66	14.3	.15	8.6	.80	4.6	14.00	1.9
.68	45.9	.68	22.7	.68	14.2	.20	8.4	.90	4.5	14.50	1.8
1.70	45.1	2.70	22.5	3.70	14.0	5.25	8.3			15.00	1.7
.72	44.3	.72	22.3	.72	13.9	.30	8.2			15.50	1.6
.74	43.5	.74	22.1	.74	13.8	.35	8.1				
.76	42.7	.76	21.8	.76	13.7	.40	8.0			16.00	1.6
.78	42.0	.78	21.6	.78	13.6	.45	7.9			16.50	1.5
1.80	41.4	2.80	21.3	3.80	13.5	5.50	7.8	8.00	4.4		
.82	40.7	.82	21.1	.82	13.4	.55	7.7	.10	4.3		
.84	40.1	.84	20.9	.84	13.3	.60	7.5	.20	4.2		
.86	39.4	.86	20.7	.86	13.2	.65	7.4	.30	4.2		
.88	38.8	.88	20.4	.88	13.1	.70	7.3	.40	4.1		
1.90	38.2	2.90	20.2	3.90	13.0	5.75	7.2	8.50	4.0		
.92	37.6	.92	20.0	.92	12.9	.80	7.1	.60	4.0		
.94	37.0	.94	19.8	.94	12.8	.85	7.0	.70	3.9		
.96	36.4	.96	19.6	.96	12.7	.90	6.9	.80	3.8		
.98	35.9	.98	19.4	.98	12.6	.95	6.8	.90	3.8		
2.00	35.3	3.00	19.2	4.00	12.5	6.00	6.8	9.00	3.7		

Figure 3. Table for converting the ratio of areas into the ratio of volumes. The value for the area of the medulla is divided into the value for the area of the whole gland. The figure corresponding to this is found in the first column and the answer is read from the second column. This last is the percentage of the whole gland by volume which is made up of medulla.

calculate the ratio between the areas expressed either in square units or as weight and then read off the answer desired in the table.

In making the calculation above described, the silhouettes of the medulla and entire gland are regarded as the projections of the outlines of solids of revolution. Such solids will be related in volume as the 3/2

power of their silhouettes since the areas vary as the squares and the volumes as the cubes of their dimensions. If we take the cube of the square roots of the areas of the entire gland and of the medulla, we shall have an approximation of the volumes of the two parts. The accuracy of this approximation will depend on how closely the adrenal and its medulla approach in shape to solids of revolution and also how closely they resemble one another in shape.

The two parts in rats and the other small animals examined have the same general shape and their outlines are convex. The shape is not entirely symmetrical, however. To compensate for this we take two views of these parts at right angles as already described. This will include all the dimensions of the gland and, by averaging the results obtained from these two views, we will get figures which give an accurate picture of the relations between the two parts.

These are proportions and not absolute values. If the gland has been weighed, as suggested at the time of removal from the animal, such a proportion can be used to estimate the weights of the two parts, on the assumption that cortical and medullary material have the same specific gravity.

ACCURACY

To test the accuracy within the method, two sets of two silhouettes each were traced from a series of 19 glands. The two sets were used independently to calculate the medulla values. The average medulla value given by one set differed from that derived from the other set by less than 0.03 per cent.

To test the agreement between the silhouette and reconstruction methods, 47 rat and mouse glands were projected and then serially sectioned. The relative amount of medullary tissue was calculated for each gland by both methods. The results for individual glands did not agree closely. The results for the three groups into which the observations fell (18 mouse and 10 and 19 rat glands, respectively) always showed a higher value for the medulla as determined by the silhouette method. Correction factors were tested and it was found that, when 8.5 per cent of its value was subtracted from the medulla volume as calculated by the silhouette method, the results agreed exactly with those derived from serial sections in one series, exceeded them by 4 per cent in another and were 4 per cent too small in the third.

In the series of 19 glands, four silhouettes of each gland were traced. The usual views, X and Y, and in addition two others, W and Z (Fig. 2) at right angles to one another and one at right angles to X and Y were traced. These four views were used in place of the usual two. The medulla was 5.5 per cent too large when checked against the reconstruction results. This slightly closer agreement does not seem to justify doubling the work by using four instead of two views.

As already described, the silhouette method depends on an approximation of a volume from the outline of its largest dimensions and is, therefore, subject in theory to a greater error than the reconstruction method. This latter cannot be regarded, however, as yielding absolute values. There is the possibility of very decided errors in it, owing to the extensive manipulations through which the tissue and sections pass before they are finally traced. The most that can be hoped for in a comparison between two methods such as these is not the determination of an absolute error but the constant by which the results of the two methods differ, so that results derived from one method can be compared with those from the other.

The advantage of the silhouette method lies in the fact that a large number of specimens can be examined rapidly. Two or at most four tracings are all that are used as compared with 25 or 30 in the case of a rat adrenal for the reconstruction method. The technical work and calculations are shortened to an equal degree. The value of this is evident when one considers that the variability in the amount of medullary tissue among individual animals, such as rats, is very great and that it is necessary to examine a large number of glands before one can say that any significant deviation from the normal ratios between the two parts of the organ has occurred.

The glands are available for sectioning if further study is desired. They can be transferred from the clearing oils to cedar oil for storage. The embedded glands are brittle and the sections tend to crack. This can be overcome by using the water treatment as described in detail by Cutuly and Cutuly (8), and mentioned in Galigher's "Essentials of Practical Microtechnique" (9). The cytology and staining reactions, of course, are subject to the limitations of the fixation method used. The chromaffin reaction is excellently shown, however, and for ordinary histological work the results are satisfactory.

SUMMARY

A method has been described by which the adrenal glands of rats and mice and other small animals can be examined rapidly to determine the ratios between the medullary and cortical parts of the gland. Ten glands can be measured in the time that it takes to measure one by reconstruction.

The results when corrected by a fixed correction factor can be compared with those derived from the standard reconstruction method.

The material used for the silhouette method is available for later sectioning and microscopic study.

My grateful acknowledgements are due Doctor Eugene Cutuly, formerly of this Department and now at the Cleveland Clinic, for assistance in the technical work and also for the preparation of the table given in figure 3 and the use of figure 1.

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THE RELATIONSHIP BETWEEN THE PARATHYROID GLANDS AND SEX HORMONES IN TETANY

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It is a matter of considerable interest to students of parathyroid tetany that men are very seldom affected by the disease. In a series of 176 cases of post-thyroidectomy tetany that we have seen, only nine occurred in men and of these in only one instance was the tetany at all severe. This is even more remarkable when one reflects that thyroidectomy is performed only four times more frequently in women than in men. In a series of 88 cases of tetany, Boothby, Haines and Pemberton (1) found only one case in a man.

RELATION OF TETANY TO THE MENSES

Attacks of acute tetany frequently are closely associated with the menstrual cycle. In women with chronic tetany it is not infrequently observed that acute symptoms occur regularly at the time of menstruation and the patients may be completely free from symptoms at other times. In such cases it seems unlikely that the attack is due to loss of calcium in the menstrual blood since the attacks may regularly precede the menstrual flow. In a case of tetany observed in 1932, this point was well illustrated.

The patient was a young woman, 34 years of age, on whom five years previously hysterectomy had been performed for the removal of fibroids of the uterus. Following that time she apparently could calculate the time when the menses would have occurred because of soreness and fullness of the breasts and a sense of weight in the pelvis—symptoms which previously had accompanied her menses. Tetany developed two years later following a thyroidectomy for the removal of an adenoma of the thyroid gland. The symptoms of tetany were invariably augmented at the time the menstrual symptoms were noted, although, of course, no blood was lost.

In a study of 77 normal women, Rittman (2) found that at the time of menstruation the level of the serum calcium remained unchanged in 13 cases, was increased in 31 and decreased in 33. Okey (3) and her collaborators made a study of 12 normal women and found that a few days before menstruation there was an apparent decrease in the serum calcium which persisted for from 9 to 18 days.

We have studied the serum calcium and phosphorus levels between and during the menses in 12 normal women. The average amount of calcium between periods was 11.0 mg. per 100 cc. and during the menses 10.9 mg. per 100 cc. The phosphorus level between periods averaged 3.3 mg. per 100 cc. and during the period 3.5 mg. per 100 cc. In six cases the calcium showed an average decrease of 0.7 mg. per 100 cc. at the time of the menses.

In three there was a rise averaging 0.4 mg. and in three there was no change. Such changes may be considered as almost within the margin of error of the method employed and certainly are not of a magnitude to explain the appearance of tetany at the menstrual period.

In addition to these investigations on normal women, frequent estimations of serum calcium and phosphates in cases of tetany have been followed for periods extending through the menses. In such cases the changes in either of these constituents were not sufficient to explain the increase in symptoms at these times. (Charts 1 and 2.)

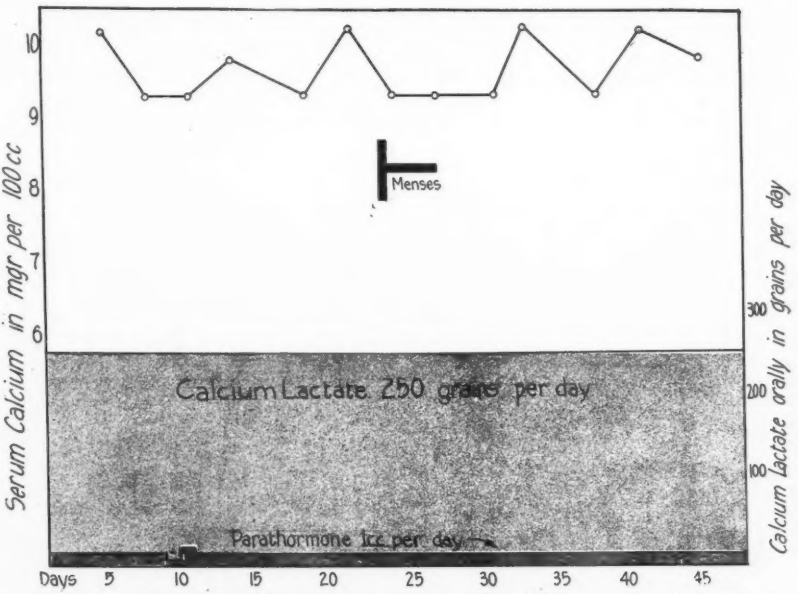

Chart 1: The relation of tetany to the menses. Note lack of any correlation between menstrual period and calcium levels.

RELATION OF TETANY TO THE MENOPAUSE

It is interesting also that in young women a more severe type of tetany occurs than in older women. We have never seen a case in a woman who had passed the menopause in which severe recurrent acute attacks of tetany were a prominent feature. In several cases of tetany in women more than fifty years of age, severe trophic changes had taken place before paresthesia or spasms had been so obvious that the necessity for treatment was recognized by the patient.

Two patients who have had parathyroid tetany for many years have been observed before, during, and after the occurrence of the menopause. In the first patient tetany developed following a thyroidectomy which was performed in 1929 when she was forty-six years of age. The serum calcium fell as low as 5.8 and the phosphates rose to 5.0 mg. per 100 cc. As long as

the menses persisted the symptoms of tetany regularly preceded the menstrual flow. Four years later, when the patient was fifty years of age, she reported that she had missed three menstrual periods and during that interval had felt much better generally. Three months later the menses recurred and were regular for three months. Symptoms of tetany occurred regularly before each menstrual period and at no other time.

The other case was that of a women in whom severe tetany developed in 1928, when she was forty-six years of age. Attacks occurred from two to five times daily and were always worse at the time of the menses. One year later treatment consisted of 225 grains of calcium lactate, 180 grains of calcium carbonate and three-fourths of one cc. of parathormone each

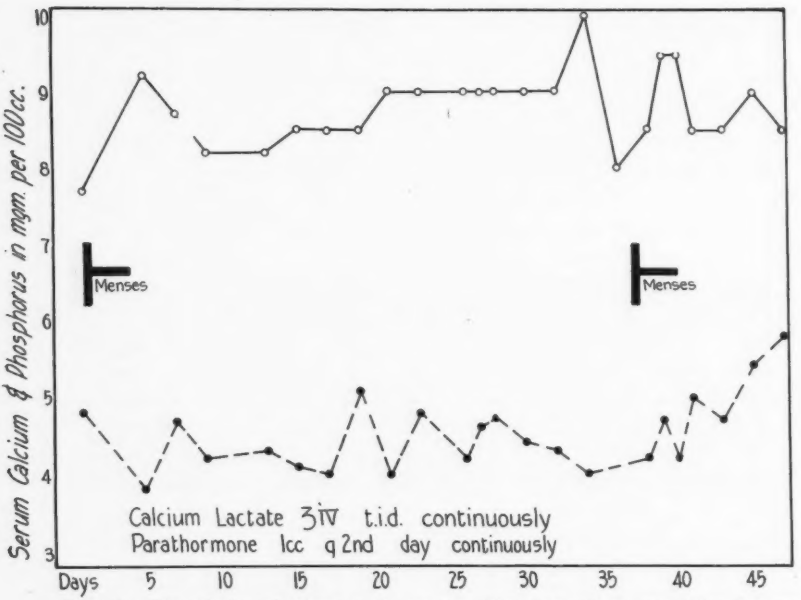

Chart 2: The relation of tetany to the menses. Note lack of any correlation between menstrual period and calcium levels.

day. In spite of these measures, severe attacks of tetany occurred frequently and intravenous injections of calcium often were necessary. The addition of 180 grams of lactose per day gave additional relief. The dose of calcium lactate was increased gradually to 720 grains per day.

In 1930 the menses stopped and have not recurred. Since that time the tetany gradually has grown less severe, but one year following the cessation of the menses all the above agents were necessary and the dosage of parathormone had been increased to 40 units twice daily.

In 1933 and 1934 she was receiving 20 units of parathormone per week and 360 grains of calcium lactate per day. Attacks of tetany still recur

but the symptoms can be controlled almost entirely by the use of 360 grains of calcium lactate per day and 1 cc. parathormone per week.

In 1923 Leicher (4) reported that he found no definite change in the levels of blood calcium before and after the menopause. In 1925 Blanchettière (5) reported an increase in calcium while Dalsace and Guillaumine (6) found that in the majority of cases serum calcium decreased after ovariectomy. In 1932, Cheymol and Quinquaud (7) reported that no change in the serum calcium followed the removal of testicles or ovaries and that in animals whose parathyroids had been removed, the subsequent removal of sex glands had no effect on the tetany.

RELATION OF TETANY TO PREGNANCY

The occurrence of tetany during pregnancy and lactation has been recognized for many years and has been thoroughly studied in the past. Frankl-Hochwart (8) reported 76 cases of tetany which occurred during pregnancy and lactation. Some of these patients had previously been subjected to operations on the thyroid gland. It has never been satisfactorily shown that the tetany of pregnancy is due to parathyroid deficiency, although Barker (9) has assumed that this disorder is due to the additional burden thrown upon the parathyroid glands.

It must be borne in mind, however, that there are excessive drains directly upon the storage of calcium at this time and the mechanism of tetany production may thus be more closely comparable with the type of tetany seen in sprue, since the stores of calcium are apparently more directly affected than are the parathyroid glands themselves.

In animals it has been shown that in the presence of experimental hypoparathyroidism no symptoms may develop during the ordinary life of the animal whereas during pregnancy tetany may develop (10, 11, 12).

In our series of cases of tetany, three patients have passed through pregnancies without any symptoms of tetany, although in each of them symptoms had been present frequently preceding the onset of pregnancy. A fourth patient with chronic tetany was seen in the sixth month of pregnancy. Previously she had had symptoms of tetany frequently but had had no symptoms during the six months she had been pregnant in spite of the fact that her treatment which consisted of 240 grains per day of calcium lactate orally had not been changed.

Findley (13) reports a case in which a woman with moderately severe tetany was able to pass through repeated pregnancies with no evidence of the disease although previously she had had as many as seven attacks in a day at the time of a menstrual period. Robert Ward (14) cites a similar instance in which a woman with tetany was freer from symptoms during two pregnancies than she was at other times, although the measures used for the control of the tetany were not altered.

It is interesting to note that Hoskins and Snyder (15) failed to find evidence in dogs that parathyroid hormone was transmitted by the placenta as indicated by any change in the serum calcium concentration of maternal

blood, following the injection of parathyroid extract into fetuses in utero. Doses as high as 120 units were used.

In our own cases, calcium values were not followed closely but in Ward's case the serum calcium during the seventh month of the second pregnancy was 6.2 mg. per 100 cc. and immediately post-partum a level of 6.4 mg. per 100 cc. was observed. Before the first pregnancy, the lowest recorded level of the serum calcium had been 6.4 mg. per 100 cc. This patient suffered from severe tetany while nursing her second child two months after delivery.

EFFECT OF INJECTION OF SEX HORMONES ON THE SERUM CALCIUM AND PHOSPHORUS IN DOGS

Normal, pregnant, and oöphorectomized dogs have received injections of varying doses of amniotin, follutein, antuitrin-S and menformon (Table 1). No consistent change in the levels of serum calcium or phosphorus were found following single injections. Normal and oöphorectomized dogs also received amniotin, menformon, follutein and antuitrin-S on five occasions over eight-day periods and no consistent variations in these minerals

TABLE 1

SERUM CALCIUM AND PHOSPHORUS LEVELS FOLLOWING A SINGLE INJECTION OF SEX HORMONE

Test Animal	Material Used	Dose		Time in Hours		
				0	6	24
				Mg.	per 100	cc.
Normal female dogs	Amniotin	2000 Ru.	Ca.	11.1	11.6	11.5
			Phos.	3.4	4.1	3.5
		4000	Ca.	11.6	11.7	11.7
			Phos.	4.7	5.7	5.1
		6000	Ca.	11.7	11.5	11.0
			Phos.	4.8	5.0	4.6
		8000	Ca.	11.3	11.8	11.0
			Phos.	4.3	4.5	4.1
Pregnant dogs	Amniotin	4000 Ru.	Ca.	11.5	10.9	11.3
			Phos.	5.1	4.3	4.9
		6000	Ca.	10.5	11.3	11.1
			Phos.	4.3	3.9	4.8
		8000	Ca.	11.3	11.4	11.5
			Phos.	4.3	4.3	4.8
Oöphorectomized dogs	Amniotin	4000 Ru.	Ca.	12.1	11.9	11.6
			Phos.	3.4	4.1	3.5
		6000	Ca.	11.6	11.9	11.8
			Phos.	4.3	4.1	4.3
		8000	Ca.	11.6	11.7	10.5
			Phos.	3.4	3.9	3.2
Normal female dogs	Follutein	1250 Mu.	Ca.	11.5	11.4	11.2
			Phos.	4.6	4.8	4.7
		2500	Ca.	11.6	11.4	11.6
			Phos.	3.9	4.0	4.1
Normal female dogs	Antuitrin-S	500 Ru.	Ca.	11.6	11.4	11.6
			Phos.	3.7	4.1	3.7
		1000	Ca.	11.8	11.5	11.6
			Phos.	4.3	4.5	4.9
Normal female dog	Menformon	5000 Mu.	Ca.	11.6	11.6	11.7
			Phos.	3.7	3.7	3.7
Oöphorectomized dog	Menformon	5000 Mu.	Ca.	11.7	11.6	11.6
			Phos.	3.7	3.8	3.8

All injections administered instramuscularly.

resulted. The variations which did occur were always within the range of the pre-experimental normals for the animals (Table 2).

TABLE 2

SERUM CALCIUM AND PHOSPHORUS LEVELS FOLLOWING FIVE INJECTIONS OF SEX HORMONE FOR EIGHT-DAY PERIODS

Test Animal	Material Used	Daily Dose	Time in Days				
			1	2	4	6	8
			Mg. per 100 cc.				
Normal female dogs.....	Amniotin.....	2000 Ru. Ca.....	11.7	11.7	11.2	11.2	11.3
		Phos...	5.0	4.0	5.0	4.8	3.3
	Menformon.....	1000 Mu. Ca.....	11.8	11.8	11.3	12.1	11.7
		Phos...	4.9	5.6	5.2	4.9	5.2
	Follutein.....	250 Mu. Ca.....	11.4	12.1	11.6	11.6	10.8
		Phos...	4.4	5.0	4.6	4.8	4.9
	Antuitrin-S.....	100 Ru. Ca.....	11.2	11.0	11.4	10.6	11.1
		Phos...	4.7	4.2	5.6	5.0	4.6
Oöphorectomized dogs	Amniotin.....	2000 Ru. Ca.....	11.0	10.9	11.2	11.6	11.8
		Phos...	4.6	4.8	4.5	4.6	5.4
	Menformon.....	1000 Mu. Ca.....	10.1	10.7	10.8	11.3	11.7
		Phos...	4.8	4.2	4.4	4.4	4.9
	Follutein.....	250 Mu. Ca.....	11.4	11.6	11.0	10.9	10.8
		Phos...	5.4	5.6	4.7	5.1	5.1
	Antuitrin-S.....	100 Ru. Ca.....	11.2	11.8	11.3	11.8	11.5
		Phos...	4.4	4.5	3.9	4.9	4.7

In some cases in which antuitrin-S has been used in the treatment of functional menorrhagia, the serum calcium and phosphorus levels have shown a tendency to increase as is shown in Chart 3.

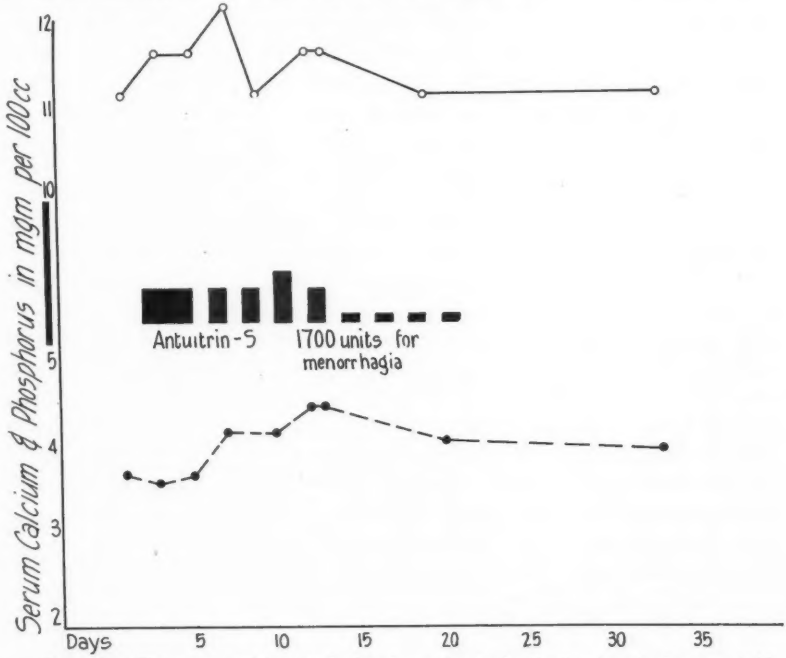

Chart 3: The serum calcium and phosphorus levels in the treatment of menorrhagia with antuitrin-S.

THE VALUE OF SEX HORMONE THERAPY IN TETANY

A case of tetany has been observed which was characterized by acute attacks of considerable severity. The tetany was never proved to be of parathyroid origin and the frequency of the attacks was apparently influenced markedly by the use of antuitrin-S. A review of this patient's case history follows:

A young woman, thirty years of age, was first examined in February, 1932. She complained of recurrent attacks of severe carpopedal spasm. The first severe attack had occurred when the patient was twenty-one years of age. These attacks first appeared at intervals of about six months, but they had increased in frequency and severity until during recent years they had recurred every two to three weeks. They almost invariably preceded the menses, and were typical tetanic seizures. There was no history of any disease of or operation on the thyroid gland.

Physical examination revealed nothing relevant to the tetanic seizures except for strongly positive Chvostek's, Trousseau's and Erb's signs. The serum calcium varied between 10.0 and 10.9 mg. per 100 cc. and the phosphates were between 2.9 and 4.2 mg. per 100 cc. in seven estimations. The amount of creatine and creatinine in the blood and urine was normal and the pH, the carbon dioxide combining power, and the level of guanidine in the blood were found to be normal on repeated estimations.

The patient had not been relieved by the administration of 40 grains of calcium lactate and one ounce of cod liver oil per day for two months. During the tetanic convulsions 20 cc. of a 10 per cent solution of calcium gluconate administered intravenously failed to influence the attack and 40 units of parathormone or 300 units of paroidin failed to give relief. Because of marked coldness and perspiration of the extremities during attacks, a lumbar sympathetic nerve block was effected on one side during one convulsion but did not affect the spasms.

For five days before the next menstrual period, 900 units of antuitrin-S were administered and for the first time in a year the patient had no tetany at the time of menstruation. Following this period, 500 units of antuitrin-S were taken and another month passed without tetany. For five months, during the ten days preceding each menstrual period, from 250 to 500 units were administered and complete freedom from tetany resulted. At that time the use of the medication was discontinued. Three months later mild symptoms recurred which abated quickly after daily injections of antuitrin-S for a week and the patient was symptom-free for three months until January, 1933. After the administration of 500 units, the symptoms again disappeared completely for four months, when a repetition of the treatment led to relief for six months.

Chvostek's and Trousseau's signs have persisted. There have been no reactions to Friedman tests and estrin assays by Kurzrok's method have indicated 4.2 and less than 4 rat units of urinary estrin per day.

A second case of tetany has been observed in which some features suggested the presence of a parathyroid factor, although this did not seem to

offer a satisfactory explanation for all the neuromuscular excitability which was present. The tetany became much less severe following the use of antuitrin-S.

The patient, a woman 36 years of age, presented herself for examination in December, 1931. In 1916 a right oöphorectomy had been performed for the removal of a cyst, and in 1925 a thyroidectomy for severe hyperthyroidism was performed. In the two years following the latter operation, definite evidence of hypothyroidism gradually developed, the basal metabolic rate in December, 1931 being minus 28 per cent. No evidence of tetany had been present for three years following the thyroidectomy, but then carpal spasm began to appear occasionally. During the few months preceding the patient's admission to the Clinic, very severe attacks of carpopedal and laryngeal spasm had occurred.

Chvostek's sign was absent but Trousseau's sign was strongly positive. The serum calcium and phosphorus were 10.6 and 2.6 mg. per 100 cc., respectively, and it is noteworthy that throughout the entire period of observation of this patient, the calcium and phosphorus levels in the blood have never been found to be abnormal. In spite of the normal calcium and phosphorus levels, each attack of tetany could be relieved promptly by an intravenous injection of 10 cc. of a 10 per cent solution of calcium gluconate. This therapeutic test appeared to indicate a relationship between the parathyroid glands and the tetany. The hypothyroidism was controlled by doses of desiccated thyroid which were gradually increased to 6 grains per day. Calcium lactate was given in doses of 2 drachms per day, alone at first and later together with 100 grains of lactose per day and the administration of ultraviolet light. There was no recurrence of any symptoms of tetany for two years. The same treatment was continued, yet six months later three extremely severe attacks of tetany occurred. Again the serum calcium and phosphorus levels were normal but because of the relief which was observed previously after the administration of calcium, the daily dose of calcium lactate was increased to 6 drachms per day. In the succeeding two months four severe tetanic seizures occurred and parathormone in doses of 10 units every second day was added to the treatment. On two occasions when a tetanic convulsion was not closely related to the menstrual time, uterine bleeding had occurred for two days following the attack.

On July 26, 1933, antuitrin-S in doses of 50 units every second day was added to the treatment. The administration of parathormone in doses of 10 units every second day was continued for six months. Since that time the patient has had no parathormone and the administration of antuitrin-S has been continued in doses of 50 units three times weekly. The dose of calcium lactate has been reduced to one drachm three times per day and except for very slight evidences on two occasions, there have been no signs of tetany. Four months later, both Chvostek's and Trousseau's signs were absent.

In this case the following facts suggest the parathyroid origin of the disease: (1) the disorder followed thyroidectomy, (2) it was improved by the use of calcium and by (3) parathormone. The facts which suggest a non-parathyroid factor of importance were: (1) unlike usual parathyroid tetany, the attacks did not appear until three years after operation, (2) serum calcium and phosphorus levels were never found to be abnormal, (3) the treatment usually effective in mild cases of parathyroid tetany was of partial benefit only and (4) there was benefit following the use of antuitrin-S.

The beneficial results seen in these two cases of tetany following the use of sex hormone therapy have not been duplicated in other cases. A case is outlined in Chart 4 in which there was severe acute postoperative

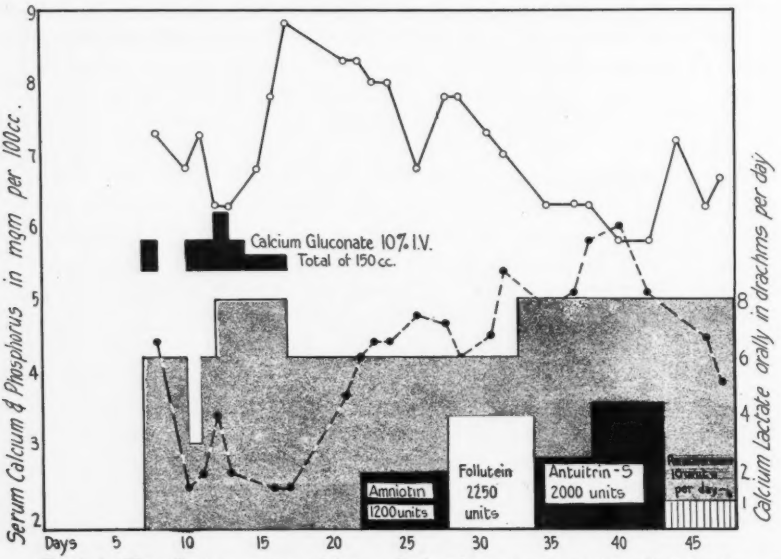

Chart 4: The effect on serum calcium and phosphorus levels of the administration of calcium gluconate, amniotin, follutein, antuitrin-S, and parathormone.

tetany. The condition was controlled by large doses of calcium orally and intravenously and the serum calcium and phosphorous levels were brought almost to normal. The subsequent use of amniotin, follutein and antuitrin-S was of no apparent benefit and it was necessary to administer parathormone which led to complete control of the symptoms.

In the case depicted in Chart 5 the use of moderate amounts of amniotin, follutein, and antuitrin-S over short periods was of no apparent benefit. However, it is interesting to note in this instance that parathormone had a decidedly greater effect between the menses than at the time of the period.

As a result of the foregoing facts and suggestive evidence, three patients with tetany have been subjected to 60 per cent of a sterilizing

dose of x-ray radiation to the ovaries. In all three cases the same treatment was carried on before and after radiation. In one case nearing the menopause, no symptoms of tetany have recurred after one year. In a second, the symptoms were completely controlled for six months and on return of the menses the symptoms of tetany also reappeared. In a third case of very severe tetany menopausal symptoms were added to the tetany which did not appear to change at all in the degree of its severity.

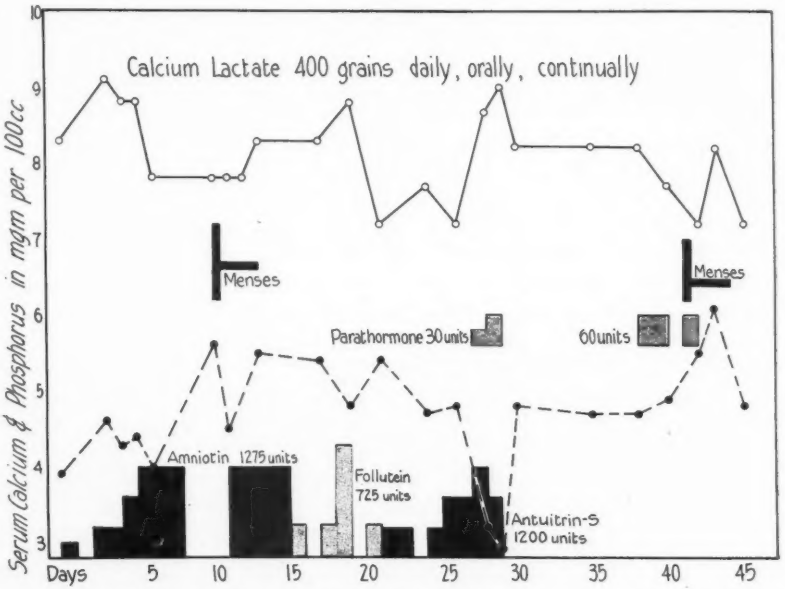

Chart 5: The effect of amniotin, follutein and antruitrin-S on serum calcium and phosphorus levels. Note that parathormone caused a greater effect between the menses than at the time of the period.

SUMMARY

The sex glands have a pronounced effect upon the neuromuscular excitability in human parathyroid tetany. Variations in amounts of sex hormones in the body were not found to be correlated with alterations in the levels of serum calcium and phosphorus and it appears probable that they affect neuromuscular excitability through a separate mechanism. The application of radiation therapy to the ovaries is suggested as a possible means of controlling some of the aggravating factors in tetany in selected cases.

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STUDIES ON THE EFFECT OF HUMAN BLOOD SERUM UPON THE GROWTH OF THE RAT*

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Early researches, with the growth hormone of the pituitary, led Evans to report its diminishing effects in the rat (1). Zondek found that the administration of the pituitary-like principle of pregnancy urine produced, at first, an increase in the size of the ovary of the rat, to be followed, in spite of continuous treatment (2), by regression to the normal. Similarly, Hertz and Hisaw and his associates (3) (4) produced a five-fold enlargement of the ovaries, of young rabbits, by injection of a sex principle of the anterior pituitary. After a certain stage of development further treatment failed to enhance the effect. Selye, Collip and Thompson (5), by means of prolonged treatment with an anterior pituitary-like preparation, recovered from pregnancy urine, obtained not only an arrest of ovary stimulation but actual regression to a size less than the normal. They also demonstrated that thyroid hyperplasia with concomitant signs of hyperthyroidism could be produced, arrested and made to regress by means of the continuous administration of a thyrotropic factor of the pituitary (6) (7). Furthermore, daily injection of serum, of treated animals, into untreated animals, not only neutralized the stimulating effect of the thyrotropic hormone but actually appeared to inhibit the metabolic functions, leading to subnormal levels of oxygen consumption (8) (9). This phenomenon was not affected by preliminary hypophysectomy and the normal sensitivity to desiccated thyroid remained the same. Considerable speculation has been aroused as to the nature of this phenomenon. Collip and his associates, who have made the most intensive study, consider it a specific antihormonal effect.

During a five-year clinical research with alkaline extracts of the anterior pituitary relatively high in the growth-promoting principle, we have noted varying degrees of refractoriness in our patients. Some of the dwarfed children, who received rather large doses of the extract, were found to be refractory from the beginning; others responded readily and continued to respond after several years of treatment. Still others, who received the extract for a year or longer, continued to grow after the extract was withdrawn at a rate exceeding that before treatment. As a rule the older the patient the more refractory he was irrespective of the status of the epiphyses. Some patients who appeared to have responded to the

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growth effect had a tendency to become moderately refractory after nine months to a year of continuous treatment. Repeated studies of the oxygen consumption and glucose utilization of this group have shed little light on the subject. Several patients had basal metabolic rates slightly lower at the end than at the beginning of treatment. One child on rather prolonged and intensive treatment developed a low glucose tolerance with glycosuria which corrected itself after the extract was withdrawn. In this study it is the growth factor with which we are principally concerned. In an attempt to determine if the inhibiting influences of whatever nature can be detected biologically and therefore used as a test of refractoriness, the following problem was outlined.

At the outset it was assumed that if the antigrowth effect was specific there should be differences between the sera of dwarfed children and that of children growing at the normal rate. Furthermore, a difference should exist between the sera of both of these groups and that of children who had received prolonged treatment. Because we intended to inject blood serum subcutaneously into the rat it was first necessary to determine how large a dose it was possible to give without producing a toxic or non-specific protein effect. Growing male rats were selected for this purpose and kept under observation on a balanced diet for twenty-one days. When the increment curve was plotted the rats were separated into two groups. One group was given 0.5 cc. adult blood serum subcutaneously, daily, while the other group was given 1 cc. They were weighed daily and the increment plotted against the control period. It was discovered that while the larger dose had a definitely inhibiting effect upon the curve, the smaller produced no change. The dosage 0.5 cc. was, therefore, chosen for the more delicate assay with different types of sera.

The main problem was divided into four parts. Seventy intact plateaued female rats were selected and their weights plotted over a period of twenty days. At the end of this time they were divided into five groups of fourteen each, the last group serving as controls.

Group I. Seven rats were given 0.5 cc. of blood serum drawn from adult patients with normal stature and no acute illness. Seven rats were given an equal amount of the same serum plus 1 cc. of an alkaline extract of the anterior pituitary relatively high in the growth-promoting principle.

Group II. Seven rats were given 0.5 cc. of blood serum drawn from dwarfs who were then receiving and had been continuously receiving (for a period from 12-36 mos.) an alkaline extract of the anterior pituitary relatively high in the growth-promoting principle (three patients). Seven rats were given an equal amount of the same serum plus 1 cc. of the pituitary extract.

Group III. Seven rats were given 0.5 cc. of blood serum drawn from dwarfed children who had previously received the alkaline extract, for many months, but who had had no treatment for a year (two patients). Seven rats were given an equal amount of the same serum plus 1 cc. of the pituitary extract.

Group IV. Seven rats were given 0.5 cc. of blood serum drawn from normally growing children who had never received treatment (six patients). Seven rats received an equal amount of the same serum plus 1 cc. of the pituitary extract.

Group V. Fourteen rats received 1 cc. of the alkaline extract of the pituitary alone.*

In all cases the injections were given daily for ten consecutive days. Daily weighings were made during the treatment and for five days there-

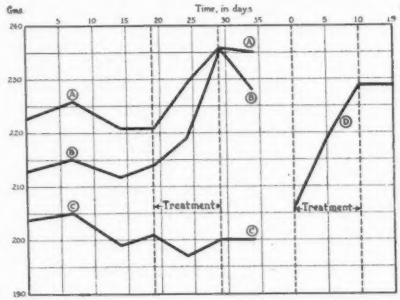

Chart 1. Group 1. Effect of human adult serum on the weight of the plateaued female rat. A. Anterior pituitary extract alone. B. Extract plus blood serum. C. Blood serum alone. D. Extract alone in rats formerly treated with blood serum.

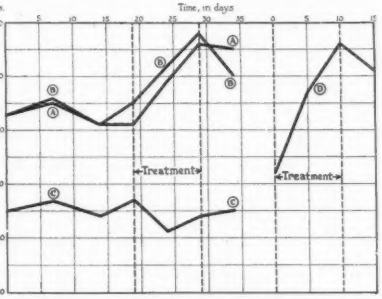

Chart 2. Group 2. Effect of blood serum of human dwarfs under treatment on the weight of plateaued female rats. A. Anterior pituitary extract alone. B. Extract plus blood serum. C. Blood serum alone. D. Extract alone in rats formerly treated with blood serum.

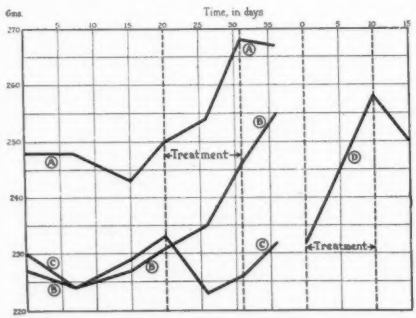

Chart 3. Group 3. Effect of blood serum of dwarfs (previously treated) on the weight of the plateaued female rat. A. Anterior pituitary extract alone. B. Extract plus blood serum. C. Blood serum alone. D. Extract alone in rats formerly treated with blood serum.

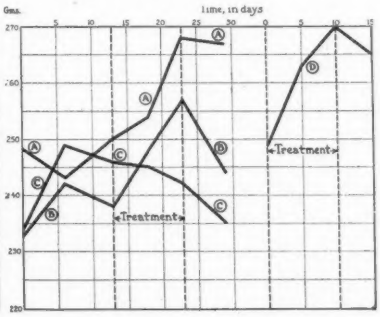

Chart 4. Group 4. Effect of blood serum of normally-growing (untreated) children on the weight of the plateaued female rat. A. Anterior pituitary extract alone. B. Extract plus blood serum. C. Blood serum alone. D. Extract alone in rats formerly treated with blood serum.

after. A surplus of food, a balanced ration, and water were allowed all groups at all times but no attempt was made to measure the actual consumption.

Chart I shows the results in Group I. The adult blood serum did not retard the growth increment as gauged by the controls. In fact, while the

*The Anterior Pituitary Extract employed in this study was supplied through the Research Department of E. R. Squibb & Sons.

TABLE 1

	Plateau Period			Treatment		Post-Treatment
	Feb. 20-27	Feb. 27-Mar. 6	Mar. 6-10	Mar. 11-15	Mar. 11-21	Mar. 11-27
Control Groups 1 and II Pituitary Extract alone	+ 3 ± 1.5	- 5 ± 1.1	+ 1 ± 2.1	+ 7 ± 4.0	+ 15 ± 5.2	+ 13 ± 3.8
Serum Group 1 (Adults)	+ 1 ± 2.3	- 6 ± 1.1	+ 2 ± 0.4	- 4 ± 1.03	- 0.6 ± 2.4	- 2 ± 2.5
Serum Group 1 plus Pituitary Extract	+ 2 ± 1.0	- 4 ± 2.5	+ 2 ± 2.1	+ 5 ± 2.4	+ 21 ± 2.8	+ 13 ± 2.1
Serum Group II (Dwarfs on Treatment)	+ 1.5 ± 1.8	- 3 ± 2.1	+ 2 ± 2.1	- 5 ± 1.7	- 2 ± 0.8	- 2 ± 2.0
Serum Group II plus Pituitary Extract	+ 3 ± 2.1	- 5 ± 1.7	+ 4 ± 1.9	+ 8 ± 1.4	+ 13 ± 3.0	+ 5 ± 2.6
	Mar. 14-22	Mar. 23-28	Mar. 29-Apr. 5	Apr. 6-10	Apr. 6-15	Apr. 6-20
Control Groups III and IV Pituitary Extract alone		- 5 ± 2.4	+ 6 ± 2.3	+ 4 ± 4.5	+ 19 ± 2.4	+ 17 ± 2.9
Serum Group III (Dwarfs - Not on Treatment)	- 5 ± 0.8	+ 4 ± 0.9	+ 4 ± 1.6	- 10 ± 1.4	- 7 ± 2.2	- 1 ± 2.1
Serum Group III plus Pituitary Extract	- 3 ± 1.4	+ 4 ± 1.0	+ 4 ± 1.0	+ 3 ± 1.3	+ 14 ± 2.4	+ 24 ± 2.2
Serum Group IV (Normally Growing Children)		+ 4 ± 0.5	- 4 ± 0.5	- 5 ± 1.0	- 3 ± 3.5	- 10 ± 4.0
Serum Group IV plus Pituitary Extract		+ 7 ± 0.6	- 3 ± 1.1	+ 10 ± 1.0	+ 19 ± 2.2	+ 6 ± 1.7

Weight increment with standard deviations, Charts 1, 2, 3, 4.

mean weight was lower at the beginning of treatment for the rats treated with serum plus hormone, they apparently grew more rapidly and reached a weight level as great as the controls. Those receiving the serum alone lost slightly in the aggregate.

Chart II shows the results in Group II. The weight curve of those receiving the blood serum of dwarfs under treatment plus the alkaline extract almost paralleled the curve of the control group. Those receiving the blood serum alone remained plateaued.

Chart III shows the results in Group III. While there was considerable discrepancy in the mean of the plateaued weights at the beginning of the experiment, those receiving the serum of dwarfed children, formerly under treatment, together with the alkaline extract, grew as rapidly as those receiving the alkaline extract alone (controls). Those receiving the blood serum alone remained plateaued.

Chart IV shows the results in Group IV. The blood serum of normal growing children neither hindered nor enhanced the stimulating power of the alkaline extract. Those receiving the serum alone lost consistently from the beginning of treatment.

Every group except IIIB, receiving the pituitary extract, lost slightly after treatment was withdrawn. This conforms with the findings of others.

Feeling that perhaps some latent antagonistic influence not encountered in the beginning would show up in the serum-treated rats, they were all subjected to injections of the pituitary extract from three to six weeks after the preliminary work had been completed. A new series of controls (plateaued females which had never received serum) were also subjected to the same quantity of the pituitary extract.

Much to our surprise all four groups of the serum-treated rats were found to be more sensitive to the growth-promoting properties of the pituitary extract than the controls. When expressed in terms of percentage, the weight increase of the serum primed over the controls was as follows: Group I, 44 per cent; Group II, 50 per cent; Group III, 62 per cent; Group IV, 31 per cent. The weight curves as compared to the control group may be seen in Chart V.

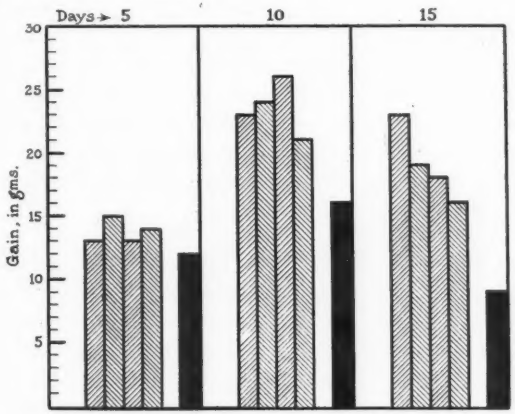

Chart 5. Growth effect of alkaline extract of anterior pituitary upon the plateaued female rat, previously treated with human blood serum. Shaded areas—Groups 1, 2, 3, 4. Solid black areas, Controls.

TABLE 2

Serum treated animals	Plateau Period			Treatment Period		Post-Treatment
	Apr. 12-18	Apr. 19-Apr.26	Apr. 27-May 6	May 6-11	May 6-16	May 6-21
Group I	- 6 ± 1.6	+ 3 ± 1.3	+ 4 ± 1.7	+ 13 ± 1.6	+ 23 ± 4.4	+ 23 ± 7.9
Group II	- 4 ± 1.8	+ 5 ± 1.9	0 ± 2.4	+ 16 ± 1.8	+ 24 ± 2.0	+ 19 ± 15.9
Group III	- 4 ± 2.2	+ 1 ± 1.3	+ 3 ± 1.3	+ 13 ± 1.7	+ 28 ± 1.2	+ 18 ± 17.9
Group IV	- 1 ± 2.2	+ 4 ± 1.3	+ 8 ± 2.8	+ 14 ± 1.6	+ 21 ± 3.5	+ 16 ± 12.2
Control Group	- 4 ± 1.3	+ 2 ± 2.3	+ 4 ± 3.0	+ 12 ± 2.5	+ 16 ± 3.5	+ 9 ± 10.8

Weight increment with standard deviations, Chart 5.

DISCUSSION

The many obvious difficulties attending such a research were known at the beginning. In the first place it was unfortunate that no more than 0.5 cc. of blood serum could be employed without producing a toxic effect on the rat. Since human adults have ceased to grow it could be argued that the retarding effects of 1 cc. of such serum produced a specific anti-hormone instead of a non-specific protein effect. If this were true, however, one would expect to see some quantitative evidence of such a phenomenon with lesser amounts or even perhaps some enhancing effect from

the sera of growing children. As a matter of fact, when the serum and pituitary extract were given concomitantly no change was encountered.

It was also felt desirable to test individuals rather than groups. Children of every description were available. In order to avoid a technical error, however, it was necessary to employ at least fourteen animals (outside of the controls) for each individual. This would have called for 7 cc. of serum or approximately 20 cc. of whole blood a day per child for ten days. The procurance of even a lesser amount from such small individuals is no easy matter. Groups were therefore selected.

Again there is the possibility that too much of the alkaline extract was employed, making it difficult for any weaker substance, such as would be contained in 0.5 cc. of blood serum, to influence its effect. Before the experiment was started, however, it was discovered that lesser amounts of the alkaline extract gave variable results in the weight increment while the effects of 1 cc. were constant.

The enhancing, rather than retarding effect of all sera on the subsequent growth of the rat is a matter for conjecture. It is possible that the administration of blood serum in some manner desensitized the animals against inherent antagonistic effects. Whatever the mechanism, the effects were clear cut and consistent.

CONCLUSIONS

Blood serum from (1) adults, from (2) dwarfed children under treatment with an alkaline extract of the anterior pituitary, from (3) dwarfed children formerly under treatment, and from (4) normally growing children, in amounts of 0.5 cc. daily, given concomitantly, did not influence the growth-promoting action of an alkaline extract of the anterior pituitary when administered to the plateaued female rat.

Blood serum from each of these groups, when administered alone, had no effect on the weight of the plateaued female rat, except in Group IV, where there was a significant loss in weight.

Rats which had previously (three to six weeks) received blood serum from all four groups were subsequently found to be more sensitive to the growth-promoting extract than rats not so treated.

It is suggested that the aforementioned may be a desensitizing effect of foreign protein upon the growth antagonistic influence inherent in the rat.

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HYPOGLYCEMIC HEADACHE*

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A problem constantly confronting the internist and general practitioner of medicine is the complaint, headache. The multiplicity of factors which contribute to the evolution of headache makes the unraveling of this symptom a major problem of differential diagnosis. Both local and systemic conditions must be considered. When several etiological factors are present simultaneously, it is difficult to evaluate the relative importance of each. The particular variety of headache known as migraine has been studied from many different points of view: those of the neurologist, the internist, the allergist, and the biochemist. Recent surveys of the problem by Riley (1) and Critchley and Ferguson (2) make another review of an exhaustive literature unnecessary. In this paper we wish to view migraine in particular, and headache in general, from what is, so far as we know, a novel point of view: that of blood sugar levels.

We have been impressed during the past few years by a change in the character of the manifestations of insulin shock as reported to us by diabetic patients. Instead of the classical symptoms of hunger, weakness, sweating, and trembling, patients now experience with increasing frequency, emotional instability, dizziness, mental confusion, and headache. The latter frequently accompanies insulin shock and may be its only manifestation. This observation naturally raises the question of what rôle, if any, hypoglycemia plays in the phenomenon of headache.

From a review of such literature as has been available we have found several notes suggesting a possible relationship between headache and hypoglycemia. Critchley and Ferguson (2) noticed the frequent occurrence of headache in the morning, after exercise, or after starvation. The finding of low blood sugar readings in children suggested transitory hypoglycemia as a factor. They prescribed glucose just before and between attacks. Hunt (3) has reported that he has been successful in relieving the headaches of a patient by prescribing one-half ounce glucose (and 3 "decholin" tablets) daily. In addition, he obtained favorable results in selected cases by the hypodermic injection of 10 to 20 minims of adrenalin (1:1000). In view of our findings to be reported below, it seems reasonable to interpret this effect as the result of the hyperglycemic action of adrenalin. Later, Critchley (4) reported finding slight hypoglycemia within the first hour or two of an attack of migraine and suggested starvation incident to anorexia and vomiting as the cause of the hypoglycemia. However, he prescribes a "full dose of glucose" for those patients whose attacks are "brought on by hunger." Wilder (5) mentions headache as a not uncom-

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mon symptom of hyperinsulinism. Rynearson and Moersch (6), in reviewing all reported cases of spontaneous hyperinsulinism (hypoglycemia), gave headache as a frequent symptom. In a complete review of the literature dealing with the neurological manifestations of insulin hypoglycemia, Jordan (7) reports headache among the common symptoms.

Since high fat (ketogenic) diets tend to lower carbohydrate tolerance (Sweeney, 8), it is no surprise that such diets should have been found to be successful in treating migraine. Barborka (9) has reported fifty cases, in 80 per cent of which the patients were benefited by ketogenic diets. Gainsborough (10) observed benefit in 78 per cent of the same number of patients with a similar diet. Bassoe (11) has prescribed cream between meals for patients who must work long hours.

HYPOGLYCEMIC MIGRAINE

From a study of a group of patients who considered headache a major complaint, it became apparent that this symptom was usually present at a time when the stomach might reasonably be expected to be empty and that many patients had learned to inhibit an impending attack by eating or drinking carbohydrate-containing foods. A group of 20 patients was found who complained of classical migraine (periodically recurring hemicrania associated with nausea and vomiting) at a time when their individual blood sugar levels were low (60-90 mg.). In them headaches could be averted by measures which kept their blood sugar level up, and relieved by the oral ingestion of food rich in carbohydrates. Only such cases in which syphilis, sinus disease, allergy, refractive errors, hypocalcemia, and definitely known cerebral disease could be excluded, were selected. Illustrative cases follow:

Case 1. G. C., an obese, married woman, 38 years old, had had unilateral headache, which recurred periodically every three to four weeks throughout her life. The headache began in the frontal area and swept over the vertex. It appeared early in the morning, usually awakening her, and lasted until 3:00 to 10:00 p.m. If it lasted until 10:00 p.m. she would vomit. During the attack she experienced scintillating scotomata. Attacks were not timed with the menses. Her family history was irrelevant. She had had a nephropexy and sterilization. The menses were always regular and normal. She had one son living and well. Physical findings were without note. Ocular, throat, nose, and ear, neurological, and x-ray examination of the sinuses, gall bladder, and chest gave negative findings. The blood pressure was 105/75. The Wassermann test findings were negative. The glucose tolerance test was reported as follows:

Hours of Glucose:	0	1	2	3	4
Blood Sugar, Mg. Per Cent (Shaeffer)	120	220	180	122	76

After the withdrawal of the fifth specimen of blood, a severe headache appeared, similar to those which she had always had. Various sedatives, pituitrin, gynergen, calcium, and elimination diets were without effect. In July, 1934, she began to take 100 cc. of orange juice daily at 4:00 a.m. No headaches occurred during the next three months. Immediately upon

omitting the orange juice they recurred, only to disappear upon resuming the treatment. She has remained free of headaches to date. The glucose tolerance test reported above was not performed until after several weeks of the treatment to be described below had been instituted. Specimens taken fasting on days when headache was present were reported to be 70 mg. per cent.

Case 2. C. A., a widow, 62 years old, had for several years experienced severe headaches at intervals of one to three weeks. Headaches had been present every day for ten days prior to admission. They began in the frontal area and spread to the occiput. They were either unilateral or bilateral, and were associated with nausea, dizziness, and vomiting. The headache usually began in the early morning and lasted until breakfast; sometimes it appeared before luncheon or dinner and lasted until she ate. The patient's mother had had migraine. In childhood she had had the usual contagious fevers; later, pneumonia and influenza. Intussusception of the bowel occurred in 1928. The menses had been regular and normal and there had been no pregnancies. The menopause had been uneventful. Physical examination was without note. The blood pressure was 120/85. Ocular, throat, nose, and ear, and x-ray examination of the sinuses gave negative findings. The blood Wassermann test findings were negative. The glucose tolerance test was reported as follows:

Hours After Glucose:	0	1	2	3	4
Blood Sugars, Mg. Per Cent (Shaeffer)	92	126	90	56	88

A typical headache occurred during the test. Various sedatives, pituitrin, and elimination diets gave no relief. Some relief was obtained from gynergen. No headache has been reported for six months since starting the dietary treatment described below.

Case 3. I. K., a thin, unmarried woman, 35 years old, had unilateral headache associated with nausea and vomiting which had recurred at regular intervals for several years. These usually appeared in the late afternoon and lasted from three to twelve hours. She had acute nephritis at 22 years of age, tonsillectomy and myomectomy (for fibroid) at 26, and antral washings at 32. Two sisters suffer from migraine. Physical findings were without note. Her eyes were correctly refracted. The blood pressure was 120/60. The blood Wassermann test findings were negative. The glucose tolerance test was reported as follows:

Hours After Glucose:	0	1	2	3
Blood Sugars, Mg. Per Cent (Shaeffer)	103	110	111	75

No relief could be obtained from sedatives or elimination diets. The results after six months of dietary treatment have been good.

In addition to those patients exhibiting the symptoms of classical migraine, others have been observed who suffer severely from various types of headache along with other symptoms. In them also the headache occurred at a time when the blood sugar level was relatively low.

Case 4. R. N., a married man, 30 years old, had had "spells" of unconsciousness for 16 years. During the past year he had in addition, suffered frequent, severe, vertical headaches, associated with weakness, sweating, and pain in the epigastrium. Ten years ago he had pleurisy, and

one year ago a vasectomy. Physical examination showed only a slight, soft enlargement of the left scrotum. The blood Wassermann test findings were negative. Ocular, throat, nose, and ear, and x-ray examination of the gastro-intestinal and gall bladder systems, and the skull were negative. Psychiatric examination unveiled a sexual maladjustment. Five glucose tolerance tests were made on different occasions, and reported as follows:

Mg. Per Cent Blood Sugar After Glucose (Folin)

Fasting	1	2	3	4
122	90	74	101	.....
112	122	94	94	.....
98	126	98	62	.....
110	92	62	102	107
100	125	107	68	.....

Reports after one year of dietary treatment show a complete cure.

Case 5. K. F., an unmarried woman, 31 years old, had experienced occipital headaches in the late afternoon during the past few years. These were associated with weakness, nervousness, and a gnawing ache in the "stomach," all of which were usually relieved by eating. At 12 years of age she had diphtheria, an appendectomy at 13, pleurisy at 15, and paratyphoid fever at 20. Tonsillectomy had been performed three times and a "chocolate" cyst removed from the ovary. The family history was irrelevant. The blood Wassermann test findings were negative. Dental caries and ichthyosis over the legs were noted during the physical examination. The glucose tolerance test was reported as follows:

Hours After Glucose:	0	1	2	3
Blood Sugar, Mg. Per Cent (Shaeffer)	105	86	80	102

Results nine months after dietary treatment are good.

It is obvious from the above reports that the blood sugar level need not fall to that which we ordinarily associate with insulin shock in order to be significant in persons disposed to headaches. The belief that a relative hypoglycemia is an accompaniment of headache in these patients is based on (1) the appearance of headache at a time when the blood sugar level was found to be or could be expected to be low, (2) the avoidance of headaches by the taking of carbohydrate-containing food several hours preceding the expected headache, and (3) a "low" or "flat" type of blood sugar curve after the ingestion of 1.5 gm. glucose per kilogram body weight. During an attack the usual blood sugar values in these patients were between 60 and 90 mg. per cent. In some of them we have been able to reproduce the headache experimentally by induced hypoglycemia. That, secondary to the initial hyperglycemia during a glucose tolerance test, has usually sufficed. Such a test, when terminated after three hours, often produced neither a significant lowering of the blood sugar nor the headache. Prolongation of the test for 4 to 6 hours is often necessary to elicit the characteristic response. We have had the opportunity occasionally of performing a glucose tolerance test during an attack of this type of migraine. The blood sugar before the administration of the glucose was, of

course, low. At the end of the first hour when the blood sugar was at its peak, the headache had subsided, to return later when the blood sugar level had again fallen.

In order to learn how frequently individuals who have a high sugar tolerance (that is, a low or flat glucose tolerance curve) suffer from headaches, we have studied the records of 111 patients showing such curves. Tests had been made on these patients for various reasons. We found that various dignoses had been recorded in their histories with neurasthenia,

TABLE 1

BLOOD SUGAR CURVES IN THIRTY-EIGHT CASES OF HEADACHE AFTER INGESTION OF 1.5 GM. GLUCOSE PER KILOGRAM BODY WEIGHT

	Case No.	Sex	Mg. Per Cent Blood Sugar Minutes After Ingestion				
			0	60	120	180	240
Migraine....	1	♀	103	110	111	75	....
	2	♀	92	126	90	56	88
	3	♀	108	108	84	84	....
	4	♀	114	110	76	....	....
	5	♀	114	100	70	76	....
	6	♀	105	86	80	102	....
	7	♀	104	98	94	88	....
			108	94	90	90	....
	8	♀	120	220	180	122	76
	9	♀	117	101	118	92	....
	10	♀	114	112	83	108	....
	11	♀	104	....	82	77	....
	12	♀	86	128	84	89	110
	13	♀	115	182	80	90	....
	14	♀	116	133	78	91	....
	15	♀	98	98	90	76	98
	16	♀	125	132	90	101	93
	17	♂	109	94	96	92	....
	18	♂	106	124	108	90	....
	19	♀	112	144	130	76	....
	20	♀	108	112	76	80	89
	21	♀	113	119	84	82	....
	22	♀	114	70	88	102	104
Other Types.	23	♂	122	90	74	101	....
			112	122	94	94	....
			98	126	98	62	....
			110	92	62	102	107
			100	125	107	68	....
	24	♂	108	100	113	86	81
	25	♂	109	94	96	92	....
	26	♂	100	106	80	80	....
	27	♂	104	84	90	90	....
	28	♀	102	88	90	98	98
	29	♀	110	84	102	101	....
	30	♀	100	182	72	76	....
	31	♀	194	118	102	86	....
	32	♀	98	132	92	50	98
	33	♀	110	102	110	110	90
	34	♀	102	120	80	52	80
	35	♀	116	120	104	88	....
	36	♀	....	114	96	62	....
	37	♀	106	178	130	62	....
	38	♀	103	198	134	65	....
Averages....	.....	.....	107	118	95	85	93

psychosis, "nervous" indigestion, spontaneous hyperinsulinism, and underweight predominating. Thirty-eight, or 34.2 per cent of the patients reported headache as a major admission complaint. Contrasted to this, only 30 of 433 diabetic patients selected at random (6.9 per cent) reported headaches. Twenty-two (19.8 per cent) of the patients in the group having low blood sugar curves, had true migraine, while only four (0.9 per cent) of the diabetic group were so afflicted. In the latter group, of course, hy-

perglycemia may be assumed. It is significant that headaches should have appeared about twenty times more frequently among a group of individuals known to have a high carbohydrate tolerance than among those known to have a low tolerance.

We have constructed a composite glucose tolerance curve, Table 1, based on the records of 38 patients. No significant difference exists between the readings of those suffering from true migraine and those suffering from other types of headache. The average readings for the group are:

Hours After Glucose:	0	1	2	3	4
Blood Sugar, Mg. Per Cent	107	118	95	85	93

Many of the patients complained of typical headache during the test at a time when their blood sugar was the lowest. Others observed a headache a few hours after completion of the test.

Considerable individual variation exists among these patients. In some, headache appears at higher levels than in others. That hypoglycemia is the sole cause of headache is not our contention. In the group studied, however, it seemed to be the trigger mechanism involved. Having demonstrated the correlation between headache and hypoglycemia, we propose to study further the mechanism of the phenomenon. Changes in water tension of the tissues, possibly the brain, induced by hypoglycemia and hyperglycemia, may be a likely clue.

Treatment. Once it has been shown that hypoglycemia is associated with the evolution of the headache, measures calculated to raise the blood sugar can be instituted. Various diet schemes have been tried. Frequent feedings are essential for all patients who suffer from this type of headache. Midmeal lunches of foods rich in carbohydrate are usually prescribed. Those individuals who suffer from headache upon awakening in the morning are instructed to awaken themselves at 4:00 a.m. and drink a glass of fruit juice or ginger ale or eat some food rich in carbohydrate. In cases 1 and 2 cited above, this treatment was quite successful. In some cases, meals predominating in fat are alternated with lunches predominating in carbohydrate. In one instance, a strict ketogenic diet (high fat meals and lunches) was successful.

THE INSULIN TOLERANCE TEST

The six-hour glucose tolerance test is cumbersome and trying to the patient. A shorter and simpler test would be desirable. This we believe has been found in the "insulin tolerance test." This test measures the fall of the blood sugar level over a certain period of time after the intravenous injection of a standard dose of insulin.*

Technique. The test is made from 12 to 16 hours after the preceding meal. Subjects remain fasting and at bed rest throughout the test. Blood specimens are taken before and at 30, 60, and 120 minutes after the intra-

*All insulin used in these experiments was kindly donated by the Frederick Stearns Company, Detroit, Michigan.

TABLE 2

BLOOD SUGAR FALL AFTER INJECTION OF INSULIN IN NORMAL CONTROLS

Case No.	Sex	Age	Mg. Per Cent Blood Sugar Minutes After Injection				Absolute Fall	Per Cent of Fasting Level
			0	30	60	120		
1.....	♂	41	80	68	58	74	22	27.5
2.....	♂	47	115	99	111	103	16	13.9
3.....	♂	42	98	94	85	79	19	19.4
4.....	♂	21	110	99	109	108	11	10.0
5.....	♂	59	138	100	127	146	38	27.5
6.....	♂	62	113	95	107	103	18	15.9
7.....	♂	37	107	94	94	121	13	12.1
8.....	♂	31	117	90	100	96	27	23.1
9.....	♂	31	118	92	100	113	26	22.0
10.....	♂	62	108	97	105	105	11	10.2
11.....	♂	35	114	87	70	110	44	38.6
12.....	♀	43	100	89	91	100	11	11.0
13.....	♀	34	114	106	114	108	8	7.0
14.....	♀	18	114	103	106	104	11	9.7
15.....	♀	15	100	94	93	127	7	7.0
16.....	♀	63	93	102	88	176	5	5.4
17.....	♀	26	90	84	83	85	7	7.8
18.....	♀	37	133	106	100	135	33	24.8
19.....	♀	26	89	125	80	80	9	10.1
20.....	♀	19	114	99	107	103	15	13.2
21.....	♀	21	127	118	108	119	19	15.0
22.....	♀	24	101	91	95	91	10	9.9
23.....	♀	53	92	70	75	84	22	23.9
24.....	♀	61	93	92	83	81	12	12.9
25.....	♀	34	100	85	87	90	15	15.0
26.....	♀	42	104	95	100	91	13	12.5
27.....	♀	34	131	58	97	132	73	55.7
28.....	♀	28	123	103	155	....	20	16.3
29.....	♀	23	98	87	104	89	11	11.2
30.....	♀	51	110	133	95	98	15	13.6
31.....	♀	68	105	95	95	87	18	17.1
32.....	♀	18	98	103	81	90	17	17.3
33.....	♀	42	132	98	120	118	34	25.8
34.....	♀	36	96	76	86	78	20	20.8
35.....	♀	55	110	88	93	78	32	29.0
						Average..	19.5±	17.5±1.13

venous injection of 0.01 unit insulin per kilogram body weight. All blood specimens are analyzed by the Folin-Wu-Malmos micro-method.† Clinical evidence of hypoglycemic shock was not noted in any patient. None complained of any inconvenience from the above dosage. We have found it safe even in arteriosclerotic subjects.

Results. The character of the fall of the blood sugar level after the intravenous injection of insulin into 35 normal individuals is recorded in Table 2. These patients were selected from the general medical service of the Santa Barbara Cottage Hospital and were free from gross clinical evidence of metabolic or endocrine disorders. The peak of the fall of the blood sugar is reached at 30 minutes after the injection of the insulin, after which the curve slowly ascends (Figure 1.) The average maximum fall for the group is 19.5 mg. glucose, and at the peak of the fall the blood sugar averages 17.5 ± 1.13 per cent below the fasting level.

Stimulated by Collip's (12) concept that the effect of the parenteral administration of any hormone is inversely proportional to its concentration in the body, we investigated a group of 29 diabetic (Table 3) and 15 "hypoglycemic" patients (Table 4). The peak of the fall in the diabetic

†It should be borne in mind that capillary blood is arterial, and that blood sugar values of 30 mg. or more higher than venous blood may be expected.

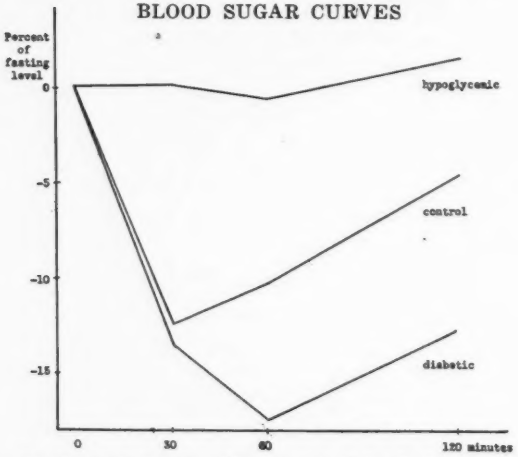

Figure 1. Blood sugar fall expressed in per cent of the fasting level following the intravenous injection of a standard dose of insulin in a group of hypoglycemic, diabetic, and normal individuals (0.01 units per kilogram body weight).

group occurred later (at 60 minutes) than in the control group (Figure 1). The absolute loss of blood sugar was 47.9 mg. glucose. At the peak of the fall the blood sugar level was 20.7 $\pm$ 1.34 per cent (Table 3) below the fasting level. This finding is in accord with the clinical precept that in diabetic patients insulin is more effective than it is in non-diabetic ones.

TABLE 3

BLOOD SUGAR AFTER INJECTION OF INSULIN IN DIABETIC PATIENTS

Case No.	Sex	Age	Mg. Per Cent Blood Sugar Minutes After Injection				Absolute Fall	Per Cent of Fasting Level
			0	30	60	120		
1.....	♂	70	230	217	208	260	22	9.6
2.....	♂	42	364	244	233	244	131	36.0
3.....	♂	38	294	285	256	263	38	12.9
4.....	♂	35	377	338	310	303	74	11.7
5.....	♂	61	273	253	238	277	35	12.8
6.....	♂	36	175	174	162	195	13	7.4
7.....	♂	44	190	160	155	163	35	18.4
8.....	♂	47	258	252	218	214	44	17.0
9.....	♂	43	204	196	180	191	24	11.8
10.....	♂	49	155	125	122	110	45	29.0
11.....	♂	61	134	126	118	117	17	12.6
12.....	♂	45	311	298	297	298	14	4.2
13.....	♂	63	377	338	310	303	74	19.6
14.....	♂	55	274	247	222	241	52	19.0
15.....	♂	48	149	122	167	150	27	18.1
16.....	♂	38	103	104	95	107	8	7.8
17.....	♂	54	143	132	143	120	23	16.1
18.....	♀	20	253	225	200	230	53	20.9
19.....	♀	60	140	130	110	117	30	21.4
20.....	♀	65	132	120	108	177	24	18.2
21.....	♀	19	358	269	294	294	89	24.9
22.....	♀	28	158	134	127	134	31	19.6
23.....	♀	9	190	178	137	128	62	32.6
24.....	♀	60	296	282	308	267	29	9.8
25.....	♀	55	229	160	156	154	75	32.8
26.....	♀	70	125	83	79	84	46	36.8
27.....	♀	69	352	257	182	168	184	52.2
28.....	♀	68	100	62	74	82	38	38.0
29.....	♀	13	186	146	134	163	52	27.9
						Average..	47.9±	20.7±1.34

TABLE 4

BLOOD SUGAR FALL AFTER INJECTION OF INSULIN IN PATIENTS WITH HYPOGLYCEMIA

Case No.	Sex	Age	Mg. Per Cent Blood Sugar Minutes After Injection				Absolute Fall	Per Cent of Fasting Level
			0	30	60	120		
1.....	♀	69	111	109	100	103	−11	−10.0
2.....	♀	41	113	....	107	95	−18	−15.9
3.....	♀	25	97	108	95	124	− 2	− 2.1
4.....	♀	62	123	108	111	131	−15	−12.2
5.....	♀	58	100	105	115	93	− 7	− 7.0
6.....	♀	44	81	79	75	72	− 9	−11.1
7.....	♂	69	101	99	108	128	− 2	− 2.0
8.....	♂	69	97	114	99	99	+ 2	+ 2.1
9.....	♂	69	101	93	90	263*	−11	−10.9
10.....	♂	31	126	118	120	118	− 8	− 6.3
11.....	♂	26	106	107	100	100	− 6	− 5.7
12.....	♂	68	78	82	89	98	+ 4	+ 5.1
13.....	♂	52	98	95	90	94	− 8	− 8.2
14.....	♀	41	103	100	124	....	− 3	− 2.9
15.....	♀	32	96	94	95	89	− 7	− 7.2
						Average.	−6.7	−6.3±0.70

*After glucose.

In order to gain a clear insight into the response of "hypoglycemic" subjects to this test, only clear-cut cases were tested. As shown in the figure the curve is nearly flat. The maximum fall occurred at 60 minutes and at its peak the blood sugar was only 6.3 ± 0.7 per cent below the fasting level. These individuals were, then, less reactive than either the controls or the diabetics. By expressing the results as per cent fall below the fasting level, variations due to differences in the actual level of the fasting blood sugar are eliminated.

The patients in this group who were free of obvious evidence of liver disease, and who exhibited abnormally low blood sugar levels after the oral ingestion of glucose, presumably had either an excess of insulin in their bodies, or such insulin as they had was inadequately antagonized. According to Collip's (12) theory, such cases should show a poor effect from the parenteral administration of additional insulin. Such was found to be the case. By the same token the subjects in the diabetic group, who presumably had an inadequate amount of insulin in their bodies, responded to the parenteral administration of additional insulin with a great effect.

DISCUSSION

Bodansky and Simpson (13) studied the effect of small doses of insulin (2 units) injected intravenously. They found that hypoglycemia appeared constantly after a brief latent period. The minimum sugar values were reached about 18 minutes after the injection. Recovery began at once and was usually complete within 30 to 40 minutes. Some difference was noted between thin and obese subjects, the recovery period of the latter being slower than that of the former.

Reiter (14) studied the blood sugar curve after the intravenous injection of 0.10 unit of insulin per kilogram body weight in five "normal" individuals. During the first half hour the blood sugar fell 22 per cent

below the fasting level which was then regained in about 60 minutes. In nine "vagotonic" subjects there was a drop of 45 per cent below the fasting level, with a return slower than in the normal group. Ten cases of obesity showed a blood sugar fall from 40 to 60 per cent below the fasting value with a slow return.

Norgaard and Thaysen (15) and Roholm and Thaysen (16) made careful studies into the effect of the intravenous injection of insulin. Their method resembles ours in that the patients were kept fasting and at bed rest during the test and that the blood sugar was determined by the micro method. A constant dose of insulin (12 units) was employed regardless of the weight of the patient. This dose exceeds any employed by us in the series reported above. A few of our subjects were given 12 units. The resulting curve differed from the one obtained by the smaller dose, only in its steeper descent. Norgaard and Thaysen (15) took blood samples every 5 to 10 minutes for the first 40 minutes, every 10 minutes for 80 minutes, and then every 15 minutes for 155 minutes. In 42 tests on 35 patients they found a straight line fall in the blood sugar for 25 minutes and then a gradual rise. Their normal cases averaged 56 per cent fall below the fasting level (35 to 79 per cent range). In the majority of the subjects tested, clinical symptoms of insulin shock developed. We believe that this fact may have masked some features of the blood sugar curve brought out by the smaller dose.

Labbé and his associates (17) have studied the reaction of a few patients suffering from various endocrine disorders with the intravenous insulin tolerance test of Norgaard and Thaysen. Normal responses were obtained in scleroderma, acromegaly, and diabetes insipidus. Increased sensitivity (as shown by alarming hypoglycemic shock) was noted in cases of Basedow's disease, von Recklinghausen's disease of bones, and Addison's disease.

Shelton (18) reports an instance of collapse during an insulin tolerance test carried out according to our method in a patient suffering from anterior lobe pituitary deficiency.

When we first began studying the effect of the intravenous administration of insulin upon the blood sugar, we used much larger doses, such as 0.50, 0.25, and 0.12 unit per kilogram body weight. We finally arrived at 0.01 unit per kilogram body weight as the smallest effective dose.

The insulin tolerance test can be applied clinically to the study of the hypoglycemic type of migraine. In several instances we have been able to predict from the character of the insulin tolerance curve that hypoglycemia was a factor in the case of migraine under consideration. A subsequent glucose tolerance test has confirmed this prediction. Conceivably, this test might also be used to differentiate between conditions due to excess of insulin and those due to inadequate mobilization of glycogen.

Until further study has revealed the limitations of the insulin tolerance test, the prolonged glucose tolerance test will probably remain the chief instrument of the clinician in diagnosing hypoglycemic states. As

stated above, the three-hour test often fails to reveal the expected drop in the blood sugar level. We have been more impressed by the constant flatness of the curves obtained on those patients studied than by the actual levels found. H. Gray (19) has compiled average blood sugar curves in normal individuals following the oral ingestion of glucose, varying from 50 gm. to 200 gm. The first hour after the glucose the blood sugar percentage was 0.12-0.15, the second hour 0.10-0.12, the third hour 0.09-0.10. Only in the third hour do these values differ from those which we found upon tabulating the curves of the 38 patients who suffered from headache, reported above. Similarly, Foster (20) found in normal human subjects blood sugar values of 82-120 mg. per cent in the first hour and 60-90 mg. per cent in the second hour after 100 gm. of glucose. The appearance of the curve in the fourth, fifth, and sixth hours may be more significant than has been appreciated heretofore.

As in insulin shock in the diabetic patient, considerable individual difference has been noted in the blood sugar levels at the time the patients have complained of headache. Ziskind (21) has observed a lag between the spinal fluid sugar and the blood sugar of epileptic patients during induced hypoglycemia. By inference, the spinal fluid sugar of patients suffering from the hypoglycemic type of migraine may remain lower than the blood sugar. Studies on this point are in progress.

SUMMARY

1. In a group of 38 patients headache was present when their blood sugar level was between 60 and 90 mg. per cent. Twenty-two of these patients suffered from true migraine.

2. Either complete relief or amelioration of the headache followed frequent feedings of carbohydrate-containing foods.

3. The characteristic headache has been reproduced by induced hypoglycemia.

4. The glucose tolerance curve of these patients is of the flat type.

5. The "insulin tolerance" test is a simple, safe, and rapid means of measuring reactivity to insulin.

6. Diabetic patients show a greater fall below the fasting level of the blood sugar and the hypoglycemic patients a lesser fall than normal patients, when subjected to an insulin tolerance test.

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MENTAL RETARDATION ASSOCIATED WITH ENDOCRINE AND NON-ENDOCRINE CONDITIONS*†

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The study of the relationship of endocrine disorders to mental retardation and to psychic changes is one of the most interesting and important phases of endocrinology. The extent to which this subject has been investigated, especially in the past decade may be gauged by the voluminous number of references in the literature. We have been able to collect statistics on approximately 10,000 cases in which this relationship was studied and there are probably many more. The incidence of endocrine disturbance in this aggregate number is variously estimated. The range is from 2.4 to 82 per cent. As examples: Larsen (1) reports 2.4 per cent; Potter (2), 8 per cent; Fry and Jaffe (3), 8 per cent; Fox (4), 10 per cent; Marinus and Kimball (5), 18.6 per cent; Eisenberg (6), 29 per cent; Szondi (7), 33 per cent, and Drouet and Hamel (8), 82 per cent. Our incidence of 40 per cent in the present series is higher than in any of the others with the exception of that of Drouet and Hamel.

This number does not include the numerous reports of behavior disturbances associated with endocrine disease. Our present communication is limited to a discussion of mental retardation.

The present report is based upon a study of the mental status and related data of 958 children observed and treated at the Endocrine Clinics of the Long Island College Hospital and Israel Zion Hospital. The patients were referred by several agencies such as the Board of Education, child welfare and social welfare organizations, private physicians and parents of other patients because of an endocrine condition irrespective of their mental status or for an endocrine investigation of a mental retardation. We divide our patients into two groups, endocrine and non-endocrine.

The endocrine class comprises 529 children presenting evidences of one of the following conditions: childhood myxedema (which we prefer to the term sporadic cretinism), hypothyroidism, adiposogenital dystrophy in boys, thyropituitary obesity (mostly in girls), anterior pituitary deficiency of growth, goiter, hypogonadism and gigantism.

There are 429 children in the non-endocrine group. As all but 20 these are mentally retarded, this group is referred to in this paper as the

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"non-endocrine mental retardation group." The disorders include mongolism, microcephalus, hydrocephalus, birth injury, spastic paraplegia, post-encephalitis, congenital syphilis, epilepsy, an unclassified group and various other non-endocrine conditions listed in Table I.

TABLE I

DISTRIBUTION OF CASES

	Male	Female	Total
Endocrine condition—			
Childhood myxedema	21	27	48
Hypothyroidism	44	40	84
Goiter	3	26	29
Adiposogenital dystrophy	165	0	165
Thyropitu.tary obesity	4	128	132
Anterior pituitary deficiency of growth	28	19	47
Giantism	1	0	1
Hypogonadism	17	2*	19
Pubertas praecox	1	3	4
	284	245	529
Non-endocrine condition—			
Mongolism	43	45	88
Birth injury, spastic paraplegia	39	21	60
Post-encephalitis	26	18	44
Brain injury in infancy or childhood	18	5	23
Microcephalus	15	16	31
Hydrocephalus	12	5	17
Congenital lues †	8	9	17
Epilepsy	9	8	17
Non-endocrine infantilism ‡	2	4	6
Dementia praecox	2	0	2
Lipodystrophy	1	1	2
Amaurotic idiocy	1	1	2
Achondroplasia	7	3	10
Unclassified	63	47	110
	246	183	429
Total number of endocrine cases	....	....	529
Total number of non-endocrine cases	....	....	429
Total number of cases	....	....	958

*Artificial result of operations.
‡Endocrine infantilism included under glands involved.
†Not included in any other disease listed.

Sex. There are 530 males (284 in the endocrine class and 246 in the non-endocrine) and 428 females (245 in the endocrine group and 183 in the non-endocrine).

Age. The ages show the following distribution:

	Endocrine	*Non-endocrine*
Below school age (under 5 years)	100	123
Above school age (16 years and above)	28	14
School age (5 to 16 years)	401	292

Purposes. The purposes of the study are to determine, if possible, the part played by the endocrine disorder in the production of mental retardation; the incidence of endocrine dyscrasia in a large group of children with mental retardation; the mental status of children in the individual endocrine diseases; the relationship of mental status to developmental growth as manifested by the time of onset of teething, walking and talking in both endocrine and non-endocrine disturbances; the relation

between mental retardation, endocrine disease, illness and trauma and the relation between congenital syphilis, endocrine disorder and mental retardation.

Method of Study. Each patient upon admission to the clinic is given a complete physical examination and special tests. For the past three years the methods of procedure and the diagnostic criteria toward the establishment of an endocrine basis have been in accordance with forms published elsewhere (9). Briefly they are as follows:

1. History of family and patient is obtained with special reference to developmental progress in both mental and physical fields; incidence of illness with special reference to the time of onset of mental retardation and/or the endocrine condition.

2. Physical examination is made with special emphasis on the presence or absence of definite endocrine signs or symptoms. This includes neurological studies when indicated.

3. Laboratory and chemical studies are carried out where possible and include bone studies, estimation of blood chlorides, uric acid, cholesterol, glucose, calcium and phosphorus; salt retention test in urine and sugar tolerance test in both blood and urine, basal metabolism and specific dynamic action. Wassermann and tuberculin tests were made in more than one-half of the cases in this series.

4. The school record of the child is obtained, stressing time of admission to school, rate of progress and record of achievement, motor co-ordination, sociability and adaptability. The social conditions at home are investigated by social service agencies where indicated.

5. A complete psychological examination has been carried out in the past three years on every child with mental retardation admitted to the clinics. These are performed either by the psychologists of the Board of Education or by members of the Department of Psychology.

The services of a psychologist were not available in the early years of this study. The determination of the mental status of the children for the purposes of this study was attempted by indirect evidence as presented by case histories, parental information and reports from public and parochial schools. The latter was based in part in many instances on actual psychometric testing. It is unnecessary to go into the difficulties or reliability of clinical data secured from all these sources.

Three categories were used: normal and advanced, definitely retarded and borderline. Borderline cases were then re-analyzed as to whether they were definitely above or below an I.Q. of 80. To test the reliability and validity of the estimation on the basis of indirect evidence, 193 children were chosen at random; 100 in the endocrine group and 93 in the non-endocrine. The proportion of each disease entity in the tested group was approximately the same as that for all cases of that disease in the total number studied. The I.Q. obtained on the test was then compared with the estimated mental status. Errors were found in that none of the chil-

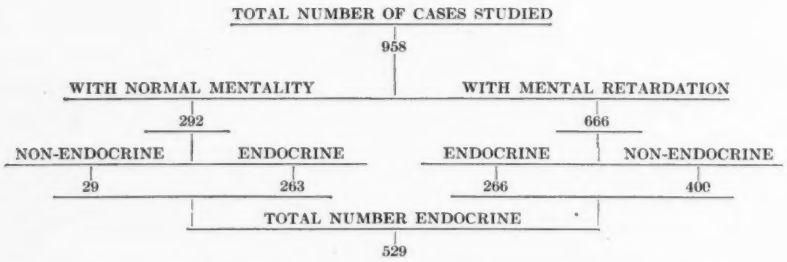
dren who tested as superior were guessed to be superior, some children guessed to be imbeciles tested as morons and some considered to be morons tested to be imbeciles. In no case, however, was a retarded child diagnosed as normal nor a normal child as retarded. We can therefore assume that the mental diagnosis made on the remainder of the children is equally valid.

6. The previous treatment with organotherapy is noted with special emphasis on the age of the patient at which it was instituted, length of time under treatment and the regularity with which it was carried out.

FINDINGS

Incidence. The distribution of the cases with reference to the mental status is shown in Table II. Of the 958 children, 292 are mentally normal

TABLE II



(263 in the endocrine group and 29 in the non-endocrine) and 666 are mentally retarded. Of this group of 666 mentally retarded children, 266 show signs of endocrine dyscrasia, an incidence of 40 per cent.

Upon the basis of the indirect method described above and on actual testing the mental status in the endocrine group is found to be distributed as follows: 50 per cent of the children have an I.Q. above 80; 21 per cent have an I.Q. of 80 to 75, and 29 per cent have an I.Q. below 75. The Board of Education endeavors to place all children with an I.Q. of 75 to 50 in ungraded classes and below 50 in special ungraded classes. There may be a small number of children in the regular grades who test below 75 but were not in ungraded classes because of lack of facilities for proper placement in certain neighborhoods.

The mental status in each endocrine disease on the basis of direct and indirect evidence is given in Table III. Mental retardation occurs with the greatest frequency in association with these diseases in the order named: childhood myxedema, hypothyroidism, adiposogenital dystrophy, thyropituitary obesity (female), anterior pituitary deficiency and goiter. Hypogonadism and giantism are not considered at this point because the selective sampling of the cases with these disorders in this series does not give a true picture.

TABLE III

Intelligence in Children With Endocrine Conditions

Condition	Number of Cases	Normal Intelligence (I.Q. 80+) No. of Cases	Retarded Intelligence		Percentage Retarded
			Backward in School But in Regular Grades* No. of Cases	In Ungraded or Special Classes† No. of Cases	
Childhood myxedema	48	1	6	41	97.9
Hypothyroidism	84	9	30	45	89.3
Goiter	29	26	0	3	10.0
Adiposogenital dystrophy	161	95	40	26	41.0
Adiposogenital dystrophy with epilepsy	3	2	0	1	33.3
Adiposogenital dystrophy with microcephalus	1	0	0	1	100.0
Anterior pituitary deficiency growth	47	38	8	1	19.0
Giantism	1	0	0	1	100.0
Thyropituitary obesity	132	84	23	25	36.0
Hypogonadism	19	6	3	10	68.4
Pubertas praecox	4	2	1	1	50.0
Total number	529	263	111	155	....
Total percentage	100	50	21	29	50

*In regular grades but considered to be backward or dull. Some of these children may have had an I.Q. below 75 but were not in ungraded classes because of lack of proper facilities.

†Definitely retarded on direct or indirect evidence; this group also contains children who were refused admission to school because of low I.Q.; also some mentally retarded who were above or below school age.

Table IV shows the average and range of the intelligence quotient on actual testing in 193 children in both the endocrine and non-endocrine groups. It will be noted that the frequency of mental retardation in the various endocrinopathies on the basis of actual tests is similar to that based on both direct and indirect evidence.

In the non-endocrine group, 6.7 per cent have an I.Q. above 80 and 93.3 per cent below that on both direct and indirect evidence. On direct testing of representative samples, 47 per cent showed an I.Q. of less than 50 in contradistinction to 11.4 per cent in the endocrine group.

TABLE IV

Average and Range of Intelligence Quotient in 193 Children Based on Actual Tests

	Average of I. Q.	Range
1. Endocrine condition—		
Childhood myxedema	59.6	40– 81
Hypothyroidism	72.5	60– 70
Thyropituitary obesity	73.4	67– 91
Adiposogenital dystrophy	75.1	37–105
Anterior pituitary deficiency	99.8	83–131
2. Non-endocrine condition—		
Mongolism	41.3	28– 65
Congenital lues	51.	40– 68
Unclassified mental retardation	55.9	26– 83
Post-encephalitis m. r.	66.3	43– 93
Epilepsy	73.	68–102
Spastic paraplegia	73.5	42–109
Birth injury	79.	74– 83
Behavior disorder	85.4	61–103
Brain injury in childhood or infancy	89.	88– 90
Dwarfism	105.	100–110

Endocrine cases	Mean	77.1	Standard deviation	20.38
Non-endocrine cases	Mean	62.66	Standard deviation	19.18

Developmental Rate. The relationship between the mental status, endocrine dyscrasia and the onset of teething, walking and talking was studied in 369 children of the endocrine group and from a non-endocrine viewpoint in 201 of the non-endocrine class in this series. This phase of the subject will appear in a separate communication (10). We found that mental retardation irrespective of its etiology is associated with a delay in both physical and mental developmental rate if the mental retardation occurs during the first year. Infants with mental retardation and endocrine disturbances teeth, walk and talk later than mentally normal infants in the same endocrine groups.

Children with mental retardation associated with non-endocrine antenatal conditions such as mongolism, congenital syphilis and microcephalus, cut teeth, walk and talk later than those with post-natal disorders like epilepsy, encephalitis or brain injury in childhood.

The relationship between endocrine conditions, mental retardation and delay in onset of teething, walking and talking may be as follows: (A) They all may be expression of some common factor present during antenatal or neo-natal life. (B) The glandular disturbance may be the cause of the delayed developmental rate and/or the mental retardation. (C) The delay may be due to the mental retardation irrespective of the existing endocrine disorder. On the basis of our findings in this series, it is difficult to evaluate these possible factors.

Relationship Between Mental Retardation, Endocrine Disease, Illness and Trauma. We were able to analyze the chronological relationship between the onset of mental retardation and of the endocrine disease in 130 cases of thyroid and pituitary disorders.

The mental retardation appears concomitantly with the endocrine disturbance in 51.5 per cent of 130 cases as a whole and in the individual diseases as follows: childhood myxedema, 91.7 per cent; hypothyroidism, 62.5 per cent; pituitary disorders, 36.6 per cent. The mental retardation precedes the appearance of endocrine signs in 8.5 per cent of all cases, in 4.2 per cent of those with hypothyroidism, in 12.2 per cent of pituitary disorders and in no cases with childhood myxedema. The mental retardation follows the onset of the endocrine condition in 40 per cent of all cases, in 8.2 per cent of childhood myxedema, in 33.3 per cent of hypothyroidism and in 51.2 per cent of the pituitary conditions.

Interesting data are obtained from a study of the age at which mental retardation appears in both the thyroid and pituitary groups. According to the case histories, it is manifested during the first two years of life in children with childhood myxedema, 91 per cent; with hypothyroidism, 71 per cent, and with pituitary disorders, 41 per cent. In the second to the sixth years it appears in children with childhood myxedema, 9 per cent; with hypothyroidism, 29 per cent, and with pituitary disorders, 50 per cent. In the sixth to the tenth years, mental retardation occurs in 9 per cent of the children with pituitary disturbances but in none in the thyroid group.

In analyzing the relationship of mental retardation to illness and trauma, we note that mental impairment follows an acute illness in 21 per cent of the pituitary cases, in 17 per cent of the hypothyroid and in only 8 per cent of childhood myxedema. The illnesses in the pituitary group are whooping cough, encephalitis and pneumonia. Pituitary disturbance was found in association with epilepsy in three instances, with chorea in two, with microcephalus in two, with mongolian imbecility in two, and with one instance each of amaurotic idiocy, bilateral congenital anophthalmia and cyst of the brain. In the thyroid group, the illnesses are whooping cough, scarlet fever, diphtheria, pneumonia, "jaundice," acute thyroiditis and unexplained fever.

A definite history of trauma precedes the onset of the mental retardation in the pituitary group only: in 12 per cent following a fall in infancy and in 2 per cent after trauma in childhood. There is not a single instance in this series in which mental retardation followed a fall or trauma in the thyroid group.

These findings indicate that there is a greater tendency for mental retardation associated with childhood myxedema and hypothyroidism to appear in the first two years of life. Mental retardation in association with pituitary disturbances appears to a greater extent after the second year of life.

A concomitant appearance of mental retardation and endocrine dyscrasia is found to the greatest extent in childhood myxedema, to a lesser degree in hypothyroidism and to the least extent in pituitary conditions. Mental retardation occurs more frequently after an acute illness in association with pituitary disturbance and hypothyroidism than with childhood myxedema. It is interesting to note that a history of a preceding trauma is mentioned only in the pituitary group and that the illnesses in this group are those generally associated with cerebral or central nervous system complications.

Congenital Syphilis. The incidence of congenital syphilis was studied from the viewpoint of signs and symptoms of this disease and the Wassermann reaction in 500 cases in this series: 216 in the endocrine and 284 in the non-endocrine group. There was positive proof of the existence of this disease in 12 instances in the endocrine class; distributed as follows: 5 with hypothyroidism, 3 with childhood myxedema, 2 with pituitary obesity and 2 with adiposogenital dystrophy, an incidence of 5.5 per cent of congenital syphilis in the endocrine group. This low incidence confirms our previous statements (11) that congenital syphilis plays an insignificant part in the production of endocrine disorder.

There were 23 instances of congenital syphilis in the non-endocrine mental retardation group, an incidence of 8 per cent distributed as follows: 1 with mongolian idiocy, 2 with microcephalus, 2 with hydrocephalus, 16 with mental retardation and 1 in achondroplasia and 1 case of tabes.

The mentality in the 35 cases of congenital syphilis in the entire series is as follows: normal, 6; normal with behavior changes, 2; mentally retarded, 27.

COMMENT

There are three probabilities in the relationship between mental retardation and ductless glandular disturbance: (1) The mental status is due to the endocrine disorder. (2) The mental retardation is the result of an unrelated non-endocrine factor. (3) The mental retardation and the endocrine disturbance are both due to a third common genetic cause such as developmental flaws or an acquired pathological condition. The literature and our own series furnish examples of each type.

Practically every member of the "endocrine family" has been considered as a possible etiological factor. The thyroid and pituitary glands are particularly favored but in many instances the rôle played by them is based on presumptive rather than on factual evidence.

The diagnoses are based upon variable evidence, ranging from clinical impression to the most elaborate laboratory methods. The latter include Abderhalden reaction, the interferometer, capillary appearance, gas exchange, basal metabolism, specific dynamic action, bone developmental rate, hormone tests, chemical findings in blood and urine and anthropological measurements.

A study of our series and of those reported in the literature shows that mental retardation occurs more frequently in association with congenital dysthyroidism (cretinism, childhood myxedema, congenital hypothyroidism and congenital goiter) than with any other endocrine condition. Clinical manifestations of both the endocrine and mental disturbance are present at birth or appear during the first year, with a delay in both physical and mental developmental rate.

There is much clinical and experimental evidence to indicate that the central nervous system is involved in congenital hypothyroid states. According to Krasnogorski (12), disturbances of the conditioned reflexes are found in children suffering from endocrine disturbances, the degree of impairment depending upon the amount of disturbance. The insufficient production of thyroid hormone greatly influences not only cortical but also infracortical reflexes so that in myxedema the secretory unconditional reflexes are decreased and the motor reactions are slow, inert and weak. In severe untreated cases the same characteristic changes in cortical activity are found as in congenital idiocy. An insufficient thyroid supply results in marked impairment of the functional activity of the associated mechanism of the cortex. Myxedematous children cannot make those adaptations to environmental conditions which normal children do by the formation of new conditioned responses.

Children with normal or increased thyroid activity will tend to be normal mentally. Olesen and Fernald (13) analyzed the intelligence of 3796 children in the sixth grade in the public schools of Cincinnati and state

that there is no significant difference in intelligence between children with thyroid enlargement and those with normal thyroids. Our findings in our small goiter group confirm their statement in that all but two of our patients showed a normal mentality.

The etiological relationship between mental retardation and pituitary disease is difficult to evaluate because of the anatomical position of the gland. It has been shown experimentally and clinically that lesions of the pituitary, tuber cinereum and diencephalon will each give rise to similar symptoms which are usually associated with adiposogenital dystrophy: obesity, hypogonadism, polyuria, polydipsia, and disturbances of carbohydrate and water metabolism.

An absolute differentiation between those symptoms due to pituitary disease and those due to extra-pituitary lesions is sometimes well-nigh impossible. We are inclined to believe with Hoskins (14) that "the pituitary-diencephalon mechanism normally functions as a unit susceptible to disturbances in either of its components with ultimately similar results. This implies that either the nervous or hormone component can substitute for one another."

Lesions which have been associated with this symptomatology include developmental flaws, trauma, encephalitis, tumors and cysts. Rowe (15) found in his study of children with behavior problems that certain of the pituitary cases were unquestionably due to intracranial pressure of extra-pituitary origin. The part played by the central nervous system was great as one-half of the patients in the endocrine group in his series and two-thirds of those in the non-endocrine gave evidence of some head injury. In our series a history of head trauma was present only in children in the pituitary group and in no single instance in the thyroid group. There is a definite but small group in our series in which the mental retardation and the endocrine symptoms were associated with ante-natal disease.

The rôle of encephalitis is probably greater than that shown by the actual figures as many instances of this condition may go unrecognized during the course of an acute infection. Our findings of a greater incidence of pituitary disturbances following acute infection strongly suggest the possibility of encephalitic changes in the pituitary region.

The association of pituitary disorder and epilepsy has assumed importance lately because of the relationship of each to water metabolism. There have been numerous instances reported of this association. We encountered three examples of pituitary obesity and epilepsy.

Other endocrine glands which have been considered as causative factors in epilepsy are the gonads, parathyroids, adrenals and pancreas but the exact relationship has not been established. A gonadal factor is predicated upon the onset of epilepsy at the time of puberty and the occurrence of attacks with menstruation. A parathyroid basis is claimed by those investigators who consider the convulsions produced by hyper-ventilation and by accidental removal of the parathyroids during thyroidectomy as epileptoid and not tetanoid. The adrenals have been impugned because

of the presence of changes in these glands in epileptics and also because of the ability of adrenalin injection to precipitate an attack (16).

Space will not permit a more detailed discussion of the relationship between mental retardation and endocrine disorders. As stated by Carlson (17) the question of this relationship is still a research problem. Clinical investigation must be carried out by use of standardized methods and the results of the various investigators evaluated according to standard criteria. Until proof to the contrary is adduced, it would be best to consider that mental retardation is associated with an endocrine condition and not necessarily the result of that condition.

SUMMARY

1. A study was made of 958 children of whom 292 were mentally normal and 666 mentally retarded. Of this latter number 266 or 40 per cent showed signs of endocrine disorder.

2. Fifty per cent of the children with endocrine disorders were of normal mentality and the other fifty per cent retarded, using an I.Q. of 80 as the critical value.

3. Mental retardation occurred with the greatest frequency in association with these diseases in the order named: childhood myxedema, hypothyroidism, pituitary obesity (adiposogenital dystrophy and thyropituitary type), anterior pituitary deficiency of growth and goiter.

4. Mentally retarded infants with endocrine conditions were found to cut teeth, walk and talk at a later date than mentally normal infants in the same endocrine groups. Practically all children with childhood myxedema in this series were mentally retarded and showed delay in all developmental fields.

5. In our experience mental retardation, irrespective of its etiology, is associated with a delay in both physical and mental developmental rate, if the mental retardation occurs during the first year of life.

6. There was found a greater tendency for mental retardation associated with childhood myxedema and hypothyroidism to appear in the first two years of life. Mental retardation in association with pituitary disturbances appeared to a greater extent after the second year of life.

7. A concomitant appearance of mental retardation and endocrine dyscrasia was found to the greatest extent in childhood myxedema, to a lesser degree in hypothyroidism and to the least extent in pituitary conditions. It appeared that mental retardation occurs more frequently after an acute illness in association with pituitary disturbance and hypothyroidism than with childhood myxedema. A history of trauma is present in the pituitary group only and in not a single instance in the thyroid class in this series.

8. Congenital syphilis played an insignificant part in the production of endocrine disorder (5.5 per cent). The incidence of congenital syphilis was only 8 per cent in the non-endocrine group of mental retardation.

9. On the basis of our findings, we are unable to state definitely the etiological relationship between endocrine disease and mental retardation. The subject should be studied further under uniform and controlled investigative methods.

10. Every child with mental retardation should be studied from a comprehensive endocrine viewpoint.

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ORGANOTHERAPY IN MENTAL RETARDATION ASSOCIATED WITH ENDOCRINE AND NON-ENDOCRINE CONDITIONS*†

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In previous papers we discussed mental retardation associated with endocrine and non-endocrine disorders from the viewpoints of the relationship to developmental rate, illness, trauma and other related data. The diagnostic criteria of endocrine disturbance and the estimation of the mental status were described (1), (2), (3).

In this present paper we report the effects of the treatment by organotherapy in children in both groups. We have limited this study to 317 mentally retarded children who were under observation for at least one year. Signs and symptoms of endocrine dyscrasia were present in 155 and manifestations of non-endocrine mental retardation in 162 children.

The diseases studied are those discussed in the other papers but in this communication we group childhood myxedema with hypothyroidism and adiposogenital dystrophy with thyropituitary obesity.

The ideal management and treatment of a mentally retarded child calls for the cooperation of the physician, school authorities, parents and social service agencies. With this objective, the following plan is carried out whenever feasible in the treatment of our patients.

(1) *Organotherapy.* This consists of the administration of desiccated thyroid and pituitary substance in various doses and combinations. Thyroid gland is given by mouth in initial dosage of 1/10 grain twice a day for the first week and three times a day for the third week. No medication is given during the second and fourth weeks. This alternation is adhered to with an increase in dosage every month to grain ⅛, ¼, ½ and 1. When the latter strength is reached, this is continued t.i.d. for the first three weeks of each month and discontinued for the fourth week. In some instances the thyroid is given twice a day for the first week of each month and three times a day for the second and third weeks. In a few instances the maximum dosage is increased to two grains t.i.d. We have found in the past 20 years that this cautious method affords an adequate check upon intolerance and overdosage.

In former years whole pituitary substance was administered by mouth but this has been changed in the past five years to desiccated anterior pituitary gland as a better standardized product. The initial dose of the latter

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is one grain t.i.d., increasing every month three grains a day until five grains t.i.d. is reached. The pituitary is given three times a day t.i.d. for the first three weeks of each month and then discontinued for the fourth week. In children with adiposogenital dystrophy, thyropituitary obesity or hypogonadism, anterior pituitary extract or anterior pituitary-like hormone from pregnancy urine is given by hypodermic injection, 1 cc. twice a week.

We have found that a combination of desiccated thyroid and pituitary gland substances is efficacious in disorders of both glands. The predominating glandular disturbance will govern the dosage of each substance, i.e., a greater dose of thyroid is given with a predominating hypothyroidism than with a frank hypopituitarism. In non-endocrine mental retardation the combination is prescribed empirically.

(2) *Remedial Measures.* An attempt is made to eliminate associated disabilities and defects such as malnutrition, diseased and markedly hypertrophied tonsils, orthopedic conditions, defective vision, hearing and speech, carious teeth and constitutional diseases such as syphilis, tuberculosis, rickets, etc.

(3) *Diet.* The diet in general consists of the proper caloric requirements with an adequate supply of vitamins. In all obese children a diet is ordered of about 1000 calories with high proteins, low fats and low carbohydrates with a restriction of both salt and water intake. Cod liver oil or halibut oil and viosterol are prescribed for all children under three years of age.

(4) *Educational Measures.* These aim at the development and improvement of muscular co-ordination and sense training in addition to routine academic work. The school work has for its object the social development of the child and stresses independence in work, self-control, co-ordination and cleanliness. This part of the program is carried out by teachers in the ungraded classes in various schools and consists of rhythmic drill and exercises, hand, wrist and finger manipulations and simple carpentry. We have had the whole-hearted co-operation of the Division of Ungraded Classes of the Board of Education of the City of New York and of several principals and teachers.

(5) *Conditions.* The social conditions are studied by several agencies and attempts are made to remedy the situation as needed by co-operation with the school authorities and with the medical program.

Irrespective of the efficacy of any method of treatment, the results depend upon several factors: the underlying cause, the stage or severity of the disease, the age of the patient and the regularity and length of time under treatment. It is obvious that a cure cannot be expected in mental retardation which is due to organic alteration of the brain cells.

The results of treatment in this series permit consideration from three angles: the mental status, the existing endocrine disorder in the endocrine

group and the associated conditions such as malnutrition, rickets, etc. In the majority of instances there was an improvement in both the endocrine and associated conditions. Improvement in the general physical condition was noted in the majority of the children and was due to treatment directed toward the elimination of the various disabilities and not to the administration of glandular substances. The response in the endocrine condition was, as a rule, quicker and greater than in the mental status. We may say that motor co-ordination, which is used as one of our criteria of improvement, is linked up to a great degree with the physical condition of the child and that educational progress, achievement and psychological adjustment are apparently closely related to the general intelligence of the child.

In this report we are concerned with an analysis of the results obtained in the mental status and shall not discuss the endocrine or associated conditions. For the purposes of this study, the results are divided into three groups: good, fair and poor, the evaluation being based upon the degree of improvement in mentality, psychological adjustment, motor co-ordination and educational progress. The results are considered good when the child showed a tendency to continuous improvement; fair when there had been an improvement at a slower rate with no assurance that it would be continuous, and poor when there had been no improvement at all or there had been a retrogression after an apparent improvement.

A tendency to continued improvement is noted only in those cases of mental retardation which are associated with disturbed endocrine conditions (45 per cent), the highest incidence being noted in anterior pituitary deficiency, childhood myxedema and hypothyroidism, pituitary obesity and hypogonadism in the order named. Disregarding those of hypogonadism and anterior pituitary deficiency because of the paucity of cases in this analysis, we find that the best results are obtained in thyroid cases (58 per cent) as against 30 per cent in the hypopituitary group. To insure continuous improvement, it is necessary to continue treatment for years.

The best results in the endocrine group are obtained with early recognition and early and long-continued treatment. Other things being equal, the prognosis is in inverse ratio to the age of the child at which treatment is instituted and in indirect ratio to the length of time under treatment. Better results are obtained when treatment is instituted at the age of five months than at the age of five years. Another important factor is the mental status at the time of first treatment, better results being obtained in the same endocrine group in patients with a higher intelligence level than those with a lower.

The administration of thyroid and pituitary gland will neither cure nor tend to produce a continuous improvement in mental retardation associated with non-endocrine conditions. The only disease in the latter group which responded to treatment was epilepsy but in both cases the children had an associated pituitary obesity.

RESULTS OF TREATMENT BY ORGANOTHERAPY
(Supplemented by Other Measures)

Condition	No Effect		Fair Results		Good Results		Total No. of Cases
	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	
Endocrine—							
Childhood myxedema and hypothyroidism	10	14	21	28	43	58	74
Pituitary obesity in both sexes	21	30	28	40	21	30	70
Anterior pituitary deficiency	0	0	2	33.3	4	66.6	6
Hypogonadism	1	20	2	40	2	40	5
All endocrine	32	21	53	34	70	45	155
Non-endocrine—							
Mongolism	25	69	11	31	0	..	36
Birth injury	10	77	3	23	0	..	13
Unclassified mental retardation	8	27	22	73	0	..	30
Spastic paraplegia	18	75	6	25	0	..	24
Post-encephalitis	16	66	8	33.3	0	..	24
Microcephalus	13	86	2	14	0	..	15
Hydrocephalus	8	80	2	20	0	..	10
Epilepsy	2	33.3	2	33.3	2*	33.3	6
Congenital lues	4	100	0	0	0	..	4
All non-endocrine	104	64.2	56	34.6	2	1.2	162

*Associated with pituitary obesity.

Fair results at a slower rate of improvement which will probably not be permanent were obtained in 34 per cent of the endocrine group and in 34.6 per cent of the non-endocrine. The incidence in the pituitary group was greater in this category than in the thyroid class. Transitory and apparent improvement was noted at some time in every type of non-endocrine disease except congenital syphilis. That this "improvement" was not real is attested by the figures in the "poor results" column.

Poor results were obtained in 21 per cent of all endocrine conditions and in 64.2 per cent of all non-endocrine diseases. The percentage of poor results was greater in the pituitary than in the thyroid group.

The percentage of "poor results" was greater than "fair results" in every type of non-endocrine mental retardation with the exception of the unclassified group. The poorest results in this series were obtained in the following disorders in the order named: congenital syphilis, microcephalus, hydrocephalus, birth injury, spastic paraplegia, mongolism, post-encephalitic mental retardation, unclassified types and epilepsy.

There were several instances of associated endocrine disturbance and non-endocrine mental retardation of the ante-natal type such as microcephalus, mongolism and syphilis. Invariably organotherapy produced an improvement in the endocrine symptoms but had no effect on the mental retardation or on the non-endocrine condition. In not a single instance was the I.Q. in a mongolian imbecile raised to a degree approximating normal intelligence, irrespective of the dosage employed. In no instance did we obtain any alteration in the facial expression as reported by Wieser in his method of irradiation of the hypophysis (4).

In mongolism associated with hypogonadism or adiposogenital dystrophy excellent results in the latter conditions were obtained but the child

remained an imbecile. It is interesting that of the six cases of epilepsy treated by organotherapy, improvement in both conditions was noted in two cases of associated epilepsy and pituitary obesity.

McQuarrie (5) has recently shown that an increased water balance precipitates epileptic seizures and conversely that dehydration ameliorates the condition. There is a water retention and salt retention in adiposogenital dystrophy. It is important to remember in the treatment of an associated epilepsy and pituitary obesity that the antidiuretic effect of pituitary extract must be offset by a restriction of fluids. An unlimited fluid intake results in a water retention and the production of epileptic seizures.

COMMENT

The effects of organotherapy on mental retardation cannot be adequately studied from a comparative viewpoint because of the lack of standardization in nomenclature, methods of diagnosis and criteria of improvement. Many reports fail to make definite differentiation between the effect on mental retardation, behavior disorder, endocrine dyscrasia and associated conditions.

The effect on mental retardation in both endocrine and non-endocrine groups ranges from absolute negative to almost miraculous results. There seems to be a unanimity of opinion that mental retardation in association with hypothyroid states is more amenable to treatment within certain limitations than with other endocrine disorders or with non-endocrine mental retardation. According to Krasnorgorski (6), the beneficial results of thyroid is due to direct action on the cerebral cortical cells. He found that thyroidin raises not only cortical but also infracortical excitability, that there is a favorable effect on cortical inhibition and an increase in the production of nervous energy. There is also an increased functional level due to the increase in metabolism.

The effect of thyroid substance in both groups may be that of a sedative, stimulant or irritant. It is a common experience to observe a pronounced sedative action in a hyperactive and hyperexcitable child with as small a dose as one-tenth of a grain. On the other hand, this same dose in another child may be capable of producing marked irritation of the central nervous system due perhaps to direct action on the cortical cells. The great majority of the children who reacted favorably to thyroid administration demonstrated the stimulative effect. In general, overdosage is manifested by irritative symptoms referable to the gastro-intestinal, circulatory or central nervous systems.

The poorer results with pituitary substance may be due to several factors. The preparations of this gland are not as well standardized as those of the thyroid. Each of the various hormones of the pituitary gland has its individual effect which cannot be produced in patients until individual fractionization has been obtained by the manufacturers of organotherapeutic agents. The anatomical and physiological relationship between

the pituitary gland and its surrounding structures has an important bearing on therapeusis. It is conceivable that symptoms produced by encephalitis in the mid-brain may simulate those resulting from injury or inflammation to the gland itself but the action to pituitary extracts may differ. The relation of the pituitary to other endocrine hormones such as the thyroid, adrenal, pancreas and gonads complicates the situation still further. We are able to confirm the observation of others that children with frank manifestations of childhood myxedema or hypothyroidism, irrespective of the mental status, do much better when anterior pituitary extract is added to thyroid extract. On the other hand, the combination of thyroid and pituitary glands is much more benficial in pituitary disorder than is the use of pituitary itself.

SUMMARY

1. The results are reported in the treatment of mental retardation associated with endocrine and non-endocrine disorders in 317 children, 155 of whom showed endocrine dyscrasia and 162 non-endocrine mental retardation.

2. The treatment consisted of (a) organotherapy (desiccated thyroid and pituitary gland), (b) remedial measures of associated disabilities such as chronic diseases, etc., (c) proper diet, (d) educational measures and (e) improvement of social conditions.

3. In an evaluation of the therapeutic values of each of these measures, it is felt that diet, improvement in social conditions and elimination of physical disabilities had no effect on the mental status in any child in this series. The change in mentality is due, then, to the action of organotheraphy or of the educational measures. The part played by the latter is great but since practically all of the school-age children, especially those in the lower I.Q. classes, had the benefit of a more or less standardized educational program, we must conclude that any beneficial results are to be attributed to the effects of glandular preparations.

4. The results obtained were as follows: A tendency to continued improvement was observed in 45 per cent of the endocrine group and in 1.2 per cent of the non-endocrine group. The two cases in the latter group were in children who had epilepsy associated with pituitary obesity. Fair or temporary results were obtained in 34 per cent in the endocrine and in 34.6 per cent in the non-endocrine group. Poor results were noted in 21 per cent of the endocrine group and in 64.2 per cent of the non-endocrine group.

5. A tendency to continued improvement following the administration of desiccated thyroid and pituitary glands was noted only in those cases of mental retardation which were associated with endocrine disorder. The highest incidence was noted in anterior pituitary deficiency, childhood myxedema, hypothyroidism and pituitary obesity in the order named. Better results (58 per cent) were obtained in thyroid disturbances than in the hypopituitary group (30 per cent).

6. According to our experience, the administration of desiccated thyroid and pituitary glands will neither cure nor tend to produce a continuous improvement in mental retardation associated with non-endocrine conditions. The most that can be expected are fair to temporary results.

7. It is concluded that in the treatment of associated endocrine and non-endocrine disturbance, organotherapy can be expected to produce an improvement in endocrine symptoms but very little effect on mental retardation or on the non-endocrine condition.

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INTERPRETATION OF THE LOWERED BASAL METABOLIC LEVEL*

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Of the many metabolic studies developed to aid in the diagnosis of hypothyroidism, basal metabolism remains the most valuable. Even this test with all its simplicity is frequently difficult to interpret when it is found to be persistently low in patients lacking the physical signs of hypothyroidism. With the widespread use of the test in diagnostic procedures, it has become recognized that the accepted range of normal basal metabolic rates of ±10 per cent, established in the earlier years, did not meet all the requirements for accurate clinical interpretation. Likewise it has long been known that many persons with basal rates well below the level of —10 per cent fail to be benefited by thyroid medication.

In certain well-defined physical states subnormal basal metabolism is the expected finding. Magnus-Levy (1) in 1906 first called attention to a low rate in marked inanition with the tendency to return toward normal with an improvement in nutrition. Hoskins (2) in a study of 300 cases of schizophrenia found a slight lowering of basal metabolism the rule. Furthermore, a lowered basal metabolic rate in mentally depressed states of appreciable degree is the common finding. Aside from the above conditions, however, the significance of a low basal rate in the absence of clinical hypothyroidism has been uncertain, and surely the value of thyroid therapy in these cases has been difficult to foretell. As a result many clinicians have developed the tendency to consider lightly any rate that does not descend to the level of —25 per cent.

In an effort to determine whether the response to thyroid therapy is attended by any constant clinical characteristics, a series of 136 patients, who had basal rates of —11 per cent or lower and who had been carefully observed while under thyroid medication, was reveiwed. Factors taken into consideration were the sex of the patient; the nutrition; the elicitation of a history either suggestive of or indicative of hypothyroidism, or the presence of physical signs of hypothyroidism; and the estimated function of the thyroid, pituitary, and gonadal glands as measured by their known effect on body functions.

Before considering the data, it seems well to emphasize the fact that all tests recorded were made on patients in a basal state insofar as it was possible to determine, and those patients in whom physical or mental relaxation was shown to be lacking were not included in this series. Never fewer than two studies were made in establishing the preliminary rate, and when wide discrepancies occurred, the tests were repeated until satisfactory

*Read before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, Cleveland, Ohio, June 12, 1934.

curves with only slight variations in rate were recorded. An average final reading was the rule except in those cases in which the variations were marked, and then an average of the lowest readings was recorded. Computation was from the Sanborn tables, which have been described by their authors as "fair intermediate values" between the Aub and DuBois and the Harris-Benedict normals.

The therapy in all cases reported was based on the requirement of the myxedematous patient, which was first reported by Boothby and Sandiford (3) and more recently by Thompson and Thompson (4) to range between 1½ and 4 grains of desiccated thyroid (U.S.P.) daily. An initial daily dosage of three grains of desiccated thyroid over a period of ten days was prescribed, and then this dosage was either maintained or altered in the direction indicated by the patient's general reaction. The chief guides to the interpretation of general improvement were an alleviation of symptomatology and an improvement in the physical signs of hypothyroidism when such signs were present.

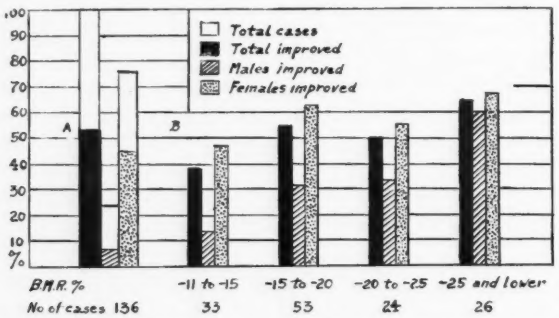

Figure 1. (A) The percentage incidence of improvement following thyroid therapy of 136 patients, 32 males and 104 females, with basal metabolic rates of —11 per cent or lower. (B) The percentage incidence of improvement in the various basal groups.

Because of the inaccuracy of basal rates in pre-adolescent children, all subjects less than 15 years of age were omitted from the analysis. No data are offered regarding age since the total number of patients in the series was insufficient to obtain reliable information when subdivided into groups in the various age limits. Considering all basal rates below —11 per cent, however, it was noted that the percentage of improvement was on the increase after the fourth decade.

RESULTS

Sex. As shown in Figure 1, but 52 per cent of all cases reviewed had shown distinct improvement. This in itself is significant only insofar as it substantiates the known fact that a basal rate of —11 per cent does not indicate the dividing line between normal and subnormal thyroid activity. Of the 52 per cent that improved, 7 per cent were males and 45 per cent were females. Corrected for the number in each sex, the relative inci-

dence of improvement was 31 per cent in the males and 59 per cent in the females.

Of more importance is a comparison of improvement at the various basal levels. Of 33 patients with basal rates of —11 to —15 per cent, improvement was noted in 39 per cent, while 55 per cent of 53 patients in the —15 to —20 per cent group were benefited, and 12 of the 24 patients, or 50 per cent, improved when the basal rate was in the range of —20 to —25 per cent. The greatest improvement occurred, as might well be expected, when the basal rate was depressed —25 per cent or more, for in this group 17 of the 26 patients, or 65 per cent, derived definite benefit.

Throughout the various groups the female patients responded more favorably than the male. This was most noticeable in the —11 to —15 per cent basal group in which only 13 per cent of the males improved as compared to 48 per cent of the females. This difference in improvement was

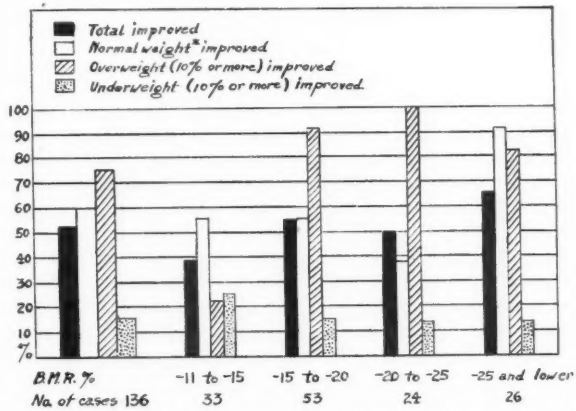

Figure 2. The percentage incidence of improvement in all patients and in those of normal weight, overweight (10 per cent or more), and underweight (10 per cent or more) in the total series and in the various basal groups.

lessened as the basal rate decreased until improvement in the two sexes closely approximated each other when the basal rate was —25 per cent or lower.

Nutrition. Patients were classified from the nutritional standpoint as normal weight, overweight, and underweight. The normal weight limits were taken from the weight standards compiled by Dr. Thomas D. Wood for the Child Health Organization, and patients were considered overweight or underweight when they exceeded these normal weight limits by 10 per cent.

In Figure 2 it is clearly shown that overweight patients led in the percentage of improvement, while only a few of the underweight patients were benefited. Normal weight patients of all groups were improved

*From weight standards as compiled by Dr. Thomas D. Wood for the Child Health Organization.

slightly less than the overweight patients. An exception to the rule worthy of note occurred in the —11 to —15 per cent group in which only 22 per cent of overweight patients were helped as compared to 56 per cent of patients whose weight fell within normal limits. Also in this same basal group the number of underweight patients to improve was greatest, totaling 25 per cent.

HISTORY AND PHYSICAL SIGNS OF HYPOTHYROIDISM

The individual equation was recognized in the interpretation of a history for hypothyroidism, and an attempt was made to follow constantly certain fundamental principles. Information was sought beginning with the birth of the patient and included the developmental history, great stress being laid on all evidence of physical retardation which could not be attributed to some other inherent or acquired cause. A single sign of retarded physical development, such as a delay in walking, a delay in

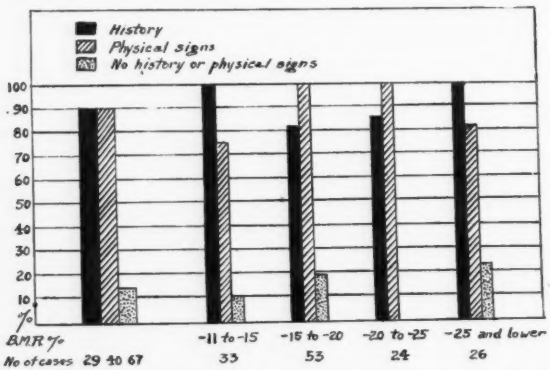

Figure 3. The percentage incidence of improvement of those patients with a history, with physical signs, and of those with neither history nor physical signs of hypothyroidism in the total series and in the various basal groups.

articulation, or a delay in any one of the other developmental features of infant life, was not considered as a criterion. However, when this single sign was coupled with one or more other suggestive signs in subsequent years of the patient's life, such as slow progress in school work, or as in the case of women, disturbances in the menses, it was given careful consideration. Fatigue, which is the most common of all complaints of hypothyroid patients, was also a prominent complaint in the non-endocrine group, and as a symptom of thyroid deficiency in itself was not considered of great importance. Other symptoms commonly found in hypothyroidism, such as somnolence, body aches, surface chilliness, paresthesias, etc., were considered of only adjuvant value in determining a positive history of hypothyroidism. Not infrequently the patient told of previous thyroid medication with relief of symptomatology, and this was considered strong evidence for a positive history.

Oftentimes physical findings of hypothyroidism were only suggestive, but only when strongly so, and only when more than one of these strongly suggestive signs were present, was the patient placed in the group along with those patients revealing unqualified physical signs of hypothyroidism. No patient was credited with having both history and physical signs in compiling the data. When both were present, the patient was placed in the group showing physical signs rather than in the group with a positive history because of the greater significance of the former.

In Figure 3 is shown the percentage incidence of improvement after thyroid therapy of those patients in whom there was a history of hypothyroidism, in whom there were physical signs of such, and in whom neither history nor physical signs were present.

It is to be noted that the percentage of improvement was slight in all basal groups when there was an absence of either history or physical findings indicating thyroid deficiency. The percentage of improvement was slightly increased in the group showing positive physical signs over the group in which a positive history was elicited, but it must be recalled that patients with physical signs were shown preference in the grouping. From these data it would appear that the presence of physical signs or the elicitation of a history of hypothyroidism, either one or both of which should go to constitute clinical hypothyroidism, is strong evidence that thyroid therapy will prove beneficial.

It is clearly seen that it is of added advantage in considering clinical hypothyroidism to include those patients with evidence of hypothyroidism in the history as well as those with physical findings. In the total series of 136 patients there were 34 classified as having unqualified hypothyroidism, the diagnosis being based chiefly on the presence of positive physical findings. An additional 29 patients gave evidence in the history of thyroid deficiency, and 40 patients showed either positive or suggestive physical signs of hypothyroidism, or a combined total of 69 patients. Improvement was noted in 62 of these 69, or in 90 per cent; while 31 of 34, or 91 per cent, of the patients with unqualified hypothyroidism were improved. Thus it is evident that many patients with thyroid deficiency will be overlooked if only those with unqualified physical signs of that condition are included under the heading of clinical hypothyroidism.

NON-ENDOCRINE AND ENDOCRINE GROUPS

Non-Endocrine Group. As shown by Figure 4, the non-endocrine group comprised 37 per cent of all cases studied. Such cases were considered in this group when there was neither history, symptomatology, physical findings, nor other data indicative of ductless gland disease other than a lowered basal metabolic rate. In all of these cases follow-up studies proved the major disorder to be of non-endocrine origin. Improvement in this group accounted for only 4 per cent of all those improved. In this respect it is worthy of note that all five that improved were in basal groups from —11 to —25 per cent and that none of the eight non-endocrine cases with

basal rates of —25 per cent or lower were benefited. Malnutrition was present in seven of these eight cases with basal metabolic rates of —25 per cent or lower, which in itself is sufficient explanation.

Endocrine Group. The endocrine group comprised 63 per cent of the entire series and accounted for 48 per cent of the total 52 per cent improved. There was an incidence of improvement of 77 per cent in the endocrine group alone. This group was composed of 34 patients each with primary thyroid and primary pituitary deficiency and 18 patients with primary gonadal hypofunction.

Thyroid. Of the 34 patients with definite clinical hypothyroidism, 31, or 91 per cent, improved on thyroid medication. Two of the three not improved had basal rates between —11 and —15 per cent, and the rate of the other one was —23 per cent. No explanation is offered for failure of these three to improve, especially the one with the basal rate of —23 per cent,

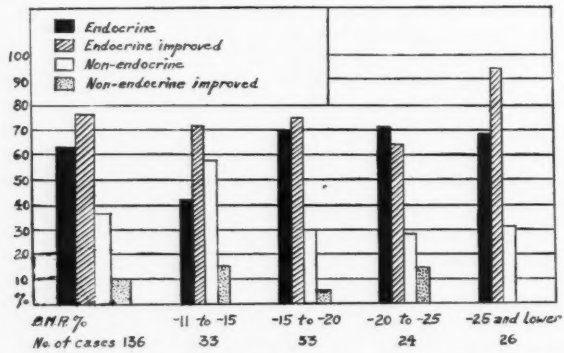

Figure 4. The percentage incidence of endocrine and non-endocrine cases and the percentage incidence of improvement of each in the total series and in the various basal groups.

for the clinical evidence was adequate for an unqualified diagnosis of hypothyroidism in all three cases, and the patients were of the type that could be depended upon for full cooperation. The basal rate in the patient having the rate of —23 per cent was not materially elevated after thyroid administration, although the dosage was considered highly adequate. This in itself suggests failure of absorption of the drug.

Pituitary. In the pituitary cases, which numbered 34, there was improvement in 68 per cent. As early as 1910 Crowe, Cushing, and Homans (5) showed that the effect of hypophysectomy on dogs pointed to a thyroid deficiency. In further experiments by Foster and Smith (6) and Smith (7) deprivation of the hypophysis in rats caused a reduction of 35 per cent in the basal metabolic rate, which could be restored to normal by daily transplants of the anterior pituitary. Additional work by Anderson and Collip (8) and many others leaves little doubt but that the pituitary gland possesses a thyroid-activating hormone. According to Foster and Smith

(6), an absence of this hormone causes atrophy of the thyroid gland, which would serve to explain not only the lowered basal metabolic rate in cases in which pituitary failure predominated, but also the improvement resulting from thyroid therapy.

Gonad. In the gonad group were included all castrates, partial and complete, menopausal cases, and those patients with sexual underfunction possessing eunuchoid characteristics. There were but 18 patients with basal rates below —11 per cent in a relatively large number of patients comprising this group. The small number prevented consideration of the individual basal groups and would indicate that relatively few gonadal cases have hypothyroidism.

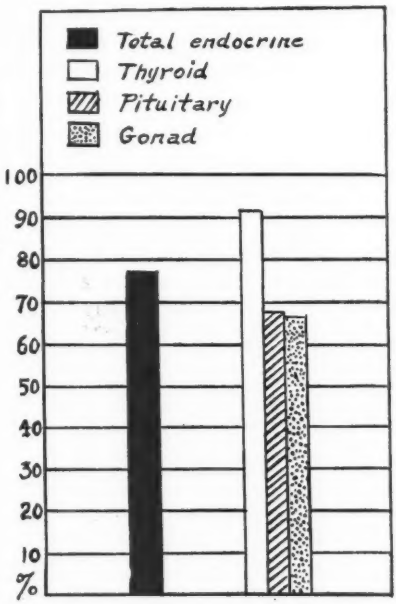

Figure 5. The percentage incidence of improvement in the entire endocrine group and in the thyroid, pituitary, and gonad cases.

Improvement in all the basal groups averaged 67 per cent. The maintenance dosage of thyroid best tolerated in the gonad group was always close to the minimum of 1½ grains a day, showing the lowered threshold of irritability of patients in this group.

BASAL RESPONSE

In most cases the basal metabolic rate was checked several times while patients were under treatment. When the basal rate was between —11 and —25 per cent, an elevation of 50 per cent or more of the basal rate was taken as the criterion for a satisfactory basal metabolic response, and when the rate was —25 per cent or lower, its elevation to within normal limits

was the accepted standard. Such a rise in the basal metabolic rate occurred in 90 per cent of all of the cases studied. Failure of absorption of the drug and mechanical error are offered as the chief suggestions for the failure of the other 10 per cent to show the expected elevation of basal metabolic rate after thyroid medication.

SUMMARY

In a series of 136 patients with basal metabolic rates of —11 per cent and lower, it was found that 52 per cent of the entire number improved on thyroid medication. When divided into groups according to basal rates, improvement occurred in 39 per cent of 33 patients with basal rates of —11 to —15 per cent; in 55 per cent with basal rates between —15 and —20 per cent; in 50 per cent with basal rates between —20 and —25 per cent, and in 65 per cent with basal rates of —25 per cent and lower. The age of the patient was not a significant factor. Women responded more favorably than men in about the ratio of 2 to 1. In general those patients who were 10 per cent or more above the normal weight limits responded more favorably than those patients who were within normal weight limits. The percentage of improvement in underweight patients was strikingly low. There were 69 patients in the series in whom the history intimated thyroid deficiency or in whom the physical findings strongly suggested that condition. In this group improvement was found to take place in an instance of 90 per cent with the presence of physical signs being slightly more significant than the elicitation of a history of hypothyroidism. Of the 34 patients with unqualified clinical hypothyroidism, improvement resulted in 31, or 91 per cent. Improvement was found to be more marked when pituitary and gonadal functions were diminished.

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THE EFFECT OF PITOCIN, PITRESSIN AND ANTUITRIN ON FAT TOLERANCE TESTS

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In a previous study (1) on fat tolerance tests it was shown that pituitary extract modified appreciably the type of blood fat curves obtained after a fat meal by preventing a significant rise or by causing a decrease in the resulting plasma cholesterol level. Since pituitary extract exhibits both oxytocic and pressor principles of the posterior lobe of the pituitary body, it appeared of interest to observe the effect of each principle on the fat tolerance.

PLAN OF STUDY

The fat tolerance was observed in a group of patients who were known to have a definite increase in the plasma cholesterol concentration following the ingestion of a fat meal. A dose of 100 gm. fat in the form of 500 cc. of 20 per cent cream was employed as a test meal. It was administered to the patients in the morning after an overnight fast. The plasma cholesterol was used as an indicator of the blood fat concentration.

The analyses were made on 2 cc. samples of plasma according to the method adopted by Bloor (2).* The tests were made in duplicate and all specimens obtained during a given test were read against the same standard. Fasting blood samples were obtained and then at two, four, six and eight hours after the fat meal was ingested.

Pitocin was employed as the solution containing the oxytocic principle of the posterior lobe of the pituitary gland, being relatively free from the pressor substances; whereas pitressin represented the pressor principle, relatively free from the oxytocic substance.

The fat tolerance tests were made on one day without pitocin or pitressin and later after several days with pitocin and pitressin administration. These were administered intranasally on a pledget of cotton in 1 cc. doses on different days immediately after the ingestion of the cream and every two hours just after the specimens of blood were taken. These tests were compared with those obtained with pituitrin of obstetrical strength administered intranasally according to the method (1) previously described.

RESULTS WITH PITOCIN AND PITRESSIN

The results of these tests are given in Table 1. There was a marked rise in the plasma cholesterol level in these individuals as the result of the fat meal but when pitocin and pitressin also were administered, compara-

*Miss Honora F. Carroll gave technical assistance.

TABLE 1

THE EFFECT OF PITUITRIN, PITOCIN AND PITRESSIN ON THE FAT TOLERANCE TESTS IN A GROUP OF PATIENTS*

Plasma Cholesterol Levels in Patients Receiving 500 cc. 20% Cream

Case	Fasting	Hours After Cream				Comment	Diagnosis
		2	4	6	8		
1	240	249	263	271	297	Control	Diabetes insipidus.
	240	243	243	253	240	Pituitrin	
	249	253	249	257	253	Pitocin	
	288	253	246	237	237	Pitressin	
2	231	246	237	260	271	Control	Diabetes insipidus.
	220	220	225	220	213	Pituitrin	
	267	246	257	267	249	Pitocin	
	225	225	220	218	215	Pitressin	
3	249	312	318	328	263	Control	Obesity.
	223	234	228	228	225	Pituitrin	
	220	228	231	223	210	Pitocin	
	249	253	243	237	234	Pitressin	
4	220	237	240	231	243	Control	Obesity.
	223	220	208	201	195	Pituitrin	
	191	203	199	199	188	Pitocin	
	205	205	195	199	197	Pitressin	
5	234	253	263	246	246	Control	Obesity.
	228	234	235	237	218	Pituitrin	
	215	231	240	199	191	Pitocin	
	191	203	191	195	187	Pitressin	
6	215	228	231	225	228	Control	Obesity.
	228	215	228	218	218	Pituitrin	
	228	223	249	237	240	Pitocin	
	246	243	228	225	195	Pitressin	
7	228	231	307	257	246	Control	Diabetes mellitus.
	234	218	223	213	213	Pitocin	
	228	234	230	249	246	Pitressin	

*The drugs were administered intranasally in 1 cc. doses immediately after the ingestion of the cream and two, four and six hours thereafter. In all the tables the plasma cholesterol is recorded in milligrams per 100 cc. of plasma.

tively little variation in the plasma cholesterol concentration was encountered. Pitocin and pitressin appeared to prevent any significant rise in the cholesterol level and at times seemed to cause a decrease in the cholesterol level below the fasting concentration. The resultant curves were similar to those found when pituitrin was administered. However, pitressin appeared to have a somewhat greater effect than pitocin and in one case pitocin did not prevent the rise in the blood cholesterol level.

COMMENT

Pitocin and pitressin administered intranasally modify appreciably like pituitrin the blood fat curves in a group of patients known to have a rise in the cholesterol level after a fat meal. They appear to decrease the plasma cholesterol concentration or prevent the development of hyperlipaemia which otherwise occurs. The explanation of the results obtained in this study are as uncertain as in the case of pituitrin. These findings may be accounted for perhaps in part by the marked increase in the fatty acids in the liver of animals which Coope and Chamberlain (3) found to be deposited following the administration of pituitary extract. The decrease in the blood fat due to pitressin possibly may be due to its effect on the intestines inhibiting the absorption of fat, but in the case of pitocin

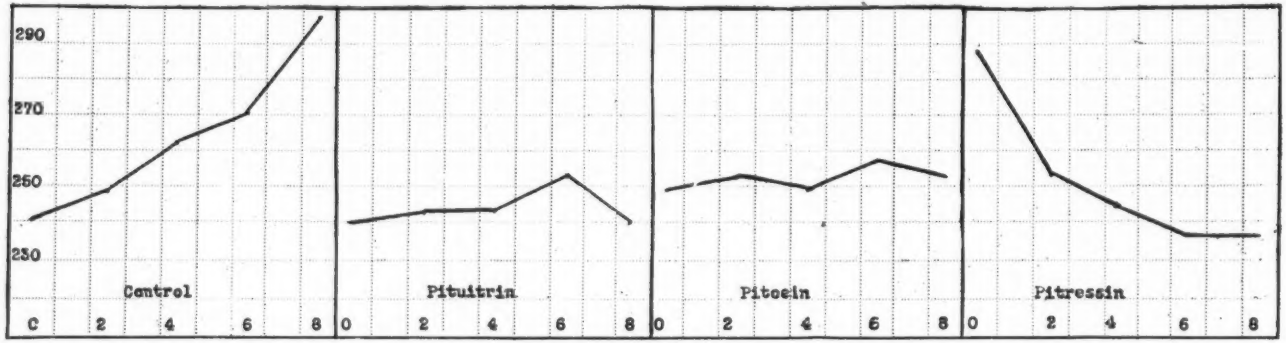

Chart 1. Relative effect of pituitrin, pitocin and pitressin on the plasma cholesterol curves in a patient with diabetes insipidus after the ingestion of 100 gm. fat. In all the charts the time interval is recorded in hours, and the plasma cholesterol in milligrams per 100 cc. of plasma.

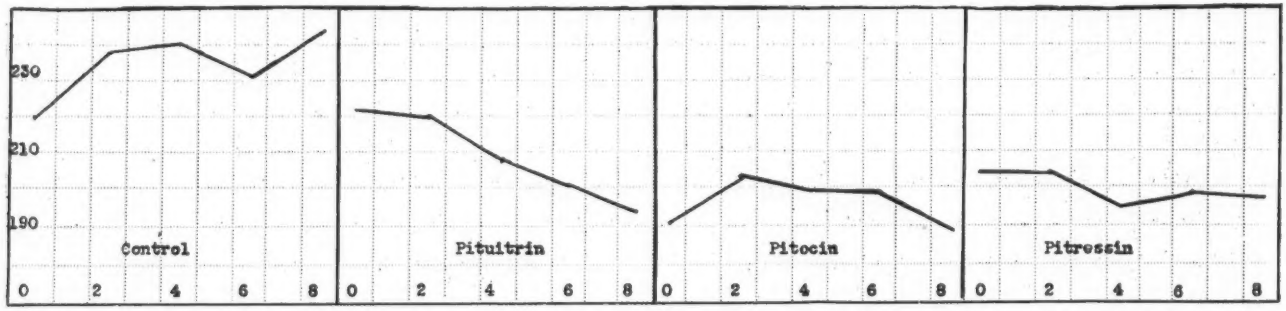

Chart 2. Relative effect of pituitrin, pitocin and pitressin on the plasma cholesterol curves in an obese patient following the intake of 100 gm. fat.

some other explanation would be necessary because this drug acts on the uterus. It would appear, then, that there is some substance common to pitressin and pitocin and present in pituitary extract which acts on fat metabolism in some other manner. However, it should be remembered that the solutions of pitocin and pitressin are not entirely free of each other.

EFFECT OF ANTUITRIN ON FAT TOLERANCE TESTS

Anselmino and Hoffman (4) have shown that a special fat metabolism hormone can be extracted from the anterior lobe of the pituitary body. The presence of such a hormone which causes a rise in the acetone bodies of the blood has been confirmed recently by Goldzieher, Sherman and Alperstein (5) and others. However, there may be an objection to term this extract a fat metabolism hormone on the basis of increasing the acetone bodies in the blood because of the possibility of its preventing the normal or complete oxidation of fat resulting in ketosis rather than mobilizing fat. On the other hand, Munoz (6) and Evans (7) have shown, respectively, that the injection of extract of the anterior lobe of the hypophysis causes an increase in the blood cholesterol and marked lipemia in dogs.

Since the extract of the anterior lobe of the pituitary is said to contain a fat hormone, it appeared of interest to check its effect on fat metabolism in a group of patients using the method of fat tolerance tests described in this paper. Antuitrin, the soluble extract of the anterior lobe of the pituitary in the form of a solution, was injected subcutaneously in 1 cc. doses immediately after the ingestion of the cream and every two hours just after the specimens of blood were taken. Incidentally, the effect of antuitrin "S," the anterior pituitary-like sex hormone obtained from the urine of pregnancy, was also tested in 1 cc. doses in the same manner.

TABLE 2

THE EFFECT OF ANTUITRIN AND ANTUITRIN-S ON FAT TOLERANCE TESTS*

Plasma Cholesterol Levels in Patients Receiving 500 cc. 20% Cream

Case	Fasting	Hours After Cream				Comment	Diagnosis
		2	4	6	8		
1	187	218	220	201	208	Control	Obesity.
	195	208	228	204	208	Antuitrin	
	187	185	191	195	213	Antuitrin S	
2	215	228	231	225	228	Control	Obesity.
	210	215	234	225	218	Antuitrin	
	203	208	215	228	210	Antuitrin S	
3	218	210	210	208	195	Control	Malnutrition.
	220	225	223	210	218	Antuitrin	
	223	215	231	228	211	Antuitrin S	
4	218	220	210	205	201	Control	Malnutrition.
	220	225	223	210	218	Antuitrin	
	223	215	231	228	211	Antuitrin S	
5	215	220	213	220	191	Control	Malnutrition.
	228	231	215	203	180	Antuitrin	
	223	228	234	225	210	Antuitrin S	

*The drugs were injected in 1 cc. doses immediately after the ingestion of the cream and two, four and six hours subsequently.

The results of these tests are given in Table 2. After the fat meal, there was some rise in the plasma cholesterol in two obese patients and a slight decrease in three malnourished patients. The administration of antuitrin and antuitrin "S" did not cause any significant change in the plasma cholesterol level in these patients, the cholesterol curves remained much the same as in the control tests.

Apparently antuitrin and antuitrin "S" did not increase the plasma cholesterol level in a small group of patients after a fat meal. The findings were so negative that the tests were not made on more patients. If antuitrin contains a fat metabolism hormone, it is not evident according to the results obtained with these fat tolerance tests.

SUMMARY

This paper presents a study of the effect of pitocin, pitressin and antuitrin on the plasma cholesterol level in a group of patients after the ingestion of a fat meal consisting of 500 cc. 20 per cent cream.

Pitocin and pitressin administered intranasally prevented a rise or caused a decrease in the plasma cholesterol levels in certain patients following the ingestion of the fat meal. These results are similar to those obtained when pituitrin was administered. Apparently there is some substance present in pitocin and pitressin, but more in the latter, which acts on fat metabolism.

Antuitrin and antuitrin "S" injected subcutaneously had no significant effect on the plasma cholesterol curves in a small group of patients after the intake of the fat meal.

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THE SIGNIFICANCE OF THE DIFFERENT TYPES OF CELLS OF THE ANTERIOR PITUITARY*

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The anterior pituitary is of great interest in many respects. Not the least interesting is the question whether the various types of cells in the anterior pituitary are separate varieties, or whether they are merely the different phases of the one type of cell. The problem that this question involves can be studied in a number of ways. For instance, histology may reveal that different types do exist and that they apparently are separate entities; but pathology requires that these cells should show some connection with some physiological or pathological process as a positive indication of their separate significance.

Up to the present, the views concerning the cells of the anterior pituitary belong to either of two groups. Those holding the one view consider that the cells represent various phases in the physiological activity of the one type of cell. In contradistinction those of the second group hold that each represents a separate type of cell with, apparently, a distinct function. In a mixed group of cases that have died from the various diseases which occur in a general hospital, one might expect to find that in a number, at least, the pituitary cells will react in a manner sufficiently distinctive to indicate which theory is the more probable. On this supposition the following investigation was undertaken.

The material which forms the basis of this present study was obtained from a series of 255 unselected cases. The diseases involved in this series were of the usual types met with in post-mortem examinations at a general hospital. The only limiting factors in the selection of the material were the condition of the body at the time of the post-mortem examination, and the time available. Each gland was divided through the center, antero-posteriorly. The sections were stained by one or several of the following methods, (1) Hemalum and Eosin, (2) Weigert's Iron Hematoxylin and Eosin, (3) Acid Fuchsin and Methyl Green.

In an investigation of this character the age and the sex incidence of the cases is essential. Equally as essential is it to determine whether or not the collection can be considered a fair sample. These points can be ascertained from Table 1, which gives the age and the sex analysis of the cases in this series, and also the corresponding figures from a series of 2000 consecutive necropsy cases, the latter serving as a control.

An examination of Table 1 shows that the age and the sex incidences of this series vary only within reasonable limits from those of the control

*Read before the Society of British Neurological Surgeons, December 1, 1934.

TABLE 1

THE AGE AND SEX INCIDENCE IN THE PITUITARY SERIES AND IN THE CONTROL SERIES

Age Group	Males			Females			Totals		
	Pituitary Series		Control	Pituitary Series		Control	Pituitary Series		Control
	No.	Per Cent	Per Cent	No.	Per Cent	Per Cent	No.	Per Cent	Per Cent
0- 1	3	1.0	0.4	0	0	0	3	1	0.4
0- 9	11	4	2	5	2	1	16	6	2.7
10-19	14	6	5	11	4	4	25	10	8.8
20-29	24	10	7	14	6	4	38	16	10.7
30-39	20	8	7	14	6	6	34	14	12.6
40-49	28	11	12	24	10	8	52	21	19.8
50-59	35	14	17	12	5	8	47	19	24.8
60-69	13	5	10	12	5	5	25	10	14.8
70	6	2	3.2	3	1	2	9	3	5.5
Total	151	61	63	95	38	37	246	..	..

group. Hence the group of cases that constitute this series can be considered a fair sample, and no allowances need be made at the later stages when making comparisons, or when drawing conclusions.

The very character of this investigation implies the use of some method for estimating the proportion of the various types of cells present. For this purpose the following method was devised and utilized throughout this investigation. The whole cell content of the anterior pituitary was given the maximum value of 10. The cell type that was least numerous was then examined, and if these were present only to the extent of a mere scattering of cells, then this particular type was given the value of 1. If, however, the cells were more plentiful and yet not numerous, then the numerical value was 2. If this particular cell type was quite numerous but not abundant then the value would be 3. If, however, the cells were abundant, then the reading would be 4, and so on. Thus it is obvious that after having obtained two readings the remaining reading could be had through simple subtraction. Usually this result was checked by a third reading.

That this method involves a large degree of the personal element is evident, and therefore the actual readings would hold good only for the individual who made that particular investigation. However, as the repeated checks showed that the results were fairly constant for that individual, it seems beyond doubt that the final deductions can be considered sufficiently reliable to form the basis for a discussion. The methods and the errors that these methods involved have been constant throughout.

The collected figures for the various age, sex and disease groups are given in the following tables. These figures are in the form of arithmetic averages. At the end of each table the combined average for each part is given. This latter figure serves as the normal reading for that part because on statistical grounds it is considered that as a large number of glands are involved there are most likely as many readings above as below the true normal. Hence the one will negate the other and the result

will be one that reasonably approaches the normal. Thus the combined results from a large number of specimens may be considered with justification to form a reliable basis for the normal standard.

TABLE 2

THE REACTION OF THE PITUITARY (PARS ANTERIOR) IN THE VARIOUS DISEASE GROUPS

Disease Group	1	2	3
Normal	3.7	2.6	3.7
Accident cases	2.3	1.5	6.2
Acute diseases	4.4	2.3	3.4
Pneumonias	5.1	2.3	2.6
Septicaemia and pyaemia	3.5	2.0	4.5
Chronic diseases	4.0	2.5	3.5
Chronic nephritis	4.0	2.0	4.0
Tumors	5.0	2.4	2.6
Thyroid disease	3.5	2.5	4.0

1. Acidophilic cells.
2. Basophilic cells.
3. Chromophobe cells.

An examination of Table 2 shows that the acidophilic cell readings are high in cases of pneumonia and of malignant disease (Susman, 1931; Wyett). In contrast, the readings obtained from the group of accident cases is definitely low. In both the pneumonia and the tumor cases the basophilic cell readings are within normal limits. However, the chromophobe cells provide readings in both groups that are definitely below the average. The accident cases display a sharp contrast, for on the one hand the readings for the acidophilic cells and the basophilic cells are low, while on the other hand, the chromophobe cell reading is very high.

The disease groups were considered first because in some of the age and the sex groups the evident variations may be due to the reaction of the gland to disease and not to any age or sex factors. The age and sex findings will be considered next.

TABLE 3

CELLS OF PARS ANTERIOR ACCORDING TO AGE AND SEX

Age Group	Males (115 Cases)			Females (67 Cases)			Total (182 Cases)		
	1	2	3	1	2	3	1	2	3
70	3.3	2.5	4.1	3.3	2.2	4.4	3.3	2.4	4.2
60	**2.6**	3.2	4.1	4.3	2.3	3.3	3.5	2.8	3.6
50	3.4	2.6	3.9	4.0	2.4	3.7	3.6	2.5	3.7
40	**4.5**	2.6	2.8	**4.6**	2.6	**2.6**	**4.6**	2.6	**2.6**
30	3.9	2.1	4.0	4.0	2.0	3.9	3.9	2.1	4.0
20	3.3	2.4	4.2	3.4	3.1	3.3	3.4	2.8	3.7
10	4.0	2.5	3.4	4.4	2.0	3.4	4.2	2.3	3.4
0	2.6	3.1	4.2	**1.9**	3.3	**4.7**	**2.2**	3.2	**4.5**
Average	3.4	2.6	3.9	3.8	2.5	3.6	3.7	2.6	3.7

1. Acidophilic cells.
2. Basophilic cells.
3. Chromophobe cells.

Table 3 shows that the acidophilic cell readings are high in the male groups between the ages of 40 and 49. Amongst the children under 10, and in the 60-year male group, the readings were low. Although the ex-

planation is not obvious, yet several points do come forward as possible factors. The low readings amongst the infants probably are due to the unstable condition of their endocrines as a whole. In this respect the pituitary does not appear to be an exception. The low reading in the 60-year group can be explained the more readily on a pathological basis. At a previous stage of this enquiry the evidence clearly indicated that in those cases exposed to shock the acidophilic cell reading was lowered and the chromophobe cell reading was correspondingly increased. As the greater proportion of the cases of the 60-year group had died of cerebral haemorrhage, shock may have been a factor. The presence of shock in these cases, therefore, may be the explanation for the low acidophilic cell reading noted.

In the 40-year groups the acidophilic cell readings were definitely above the average. As this variation is common to males and females alike some physiological explanation may be possible. That some bodily changes may occur at about 40 years of age is well known, and at this general re-adjustment stage which may be requiring the greater cooperation of the pituitary than was necessary during the earlier stages of life. At this period, too, malignant disease acquires a prominent incidence. Hence two possible points emerge, namely, that the physiological adjustments of early middle age increase the demands on the acidophilic cells, and at the same period malignant disease becomes prominent. In the analysis of the findings in the various disease groups it became obvious that the acidophilic cell activity was associated with cell proliferation and especially with malignant disease. At this stage of the investigation a further point is disclosed in that at the so-called cancer age the acidophilic cell content of the anterior pituitary has been appreciably increased. Perhaps the latter makes possible the former.

With the exception of these few variations the readings were really quite constant throughout life. The basophilic cells show only minor variations and these are insufficient to justify any interpretation of any significance. In the chromophobe cell readings the 40-year group gave results that were appreciably below the normal. The explanation will be more evident when some further points have been considered.

In order to explore more fully the significance of the various changes that have been noted, several further groups of cases might be considered. As the basophilic cells have been considered by Zondek as the source of the sex hormone of the Zondek-Aschheim test, all the cases showing a high basophilic cell content were placed in one group and examined. In all there were 21 cases of which 16 were males and 5 females. The ages were available in 20 of the cases. See Table 4 for the grouping.

The cases in this group do not fall into any particular disease group. Table 4 shows definitely that they also do not belong to any definite age group. The importance of this latter observation lies in the fact that, as children under puberty can reasonably be considered to be sexless, then there should have been some appreciable differences in the incidence of

TABLE 4

ANALYSIS OF CASES SHOWING HIGH BASOPHILIC CELL VALUES

Age Group	No. of Cases
0– 9	2
10–19	1
20–29	3
30–39	0
40–49	6
50–59	6
60–69	1
70	1

that group in Table 4, if the basophilic cells had any connection with sex functions. Instead, the incidence as a whole is that of a fair sample.

That the females of this group constitute only 25 per cent of the whole may appear at first glance to be significant. However, in the series as a whole the females accounted for 38 per cent of the cases. The difference between the two figures is not sufficient to warrant any conclusion, especially when the number of cases in the basophilic cell group is comparatively small.

A further line of approach has still to be explored. Cushing has described a clinical syndrome which, according to him, is due to the presence in the anterior pituitary of a basophilic adenoma. If this were so, then the basophilic cells possibly might be credited with a separate secretion in spite of the negative results obtained up to the present. However, the data disclosed by a previous investigation (Susman, 1935) showed that incidental tumors occurred in the anterior pituitary. These were present in 8 per cent of the pituitaries in a series of 260 cases when only the infundibular region had been examined. Of these, 3 per cent were of the basophilic type. None of these tumors had given rise to any train of symptoms. In other words, Cushing's syndrome cannot be due to the adenomata of the pituitary when these adenomata can occur so frequently in the ordinary run of cases.

DISCUSSION

According to Saint-Remy, Benda, Stewart, and Blair Bell, the three types of cells in the anterior pituitary represent different stages in the physiological activity of the one type, while Cushing is the chief exponent of the theory that they each represent a distinct type of cell and each is responsible for a distinct secretion. In this study the general impression was that the former theory was the more practical one. In other words, the data indicated that the three types of cells represented phases in the activity of the one type, that the acidophilic cells contained the finished secretion, that the basophilic cells represented the resting phase, while the chromophobe cell was in the exhausted stage.

The theory that advocates the presence of three different types of cells failed to meet practical experience in that all the three types cells cannot be associated with some physiological process. In the foregoing

examinations the age and the sex variations required little explanation. However, those variations observed amongst the disease groups need further consideration. The acidophilic cell readings in the tumor cases were well above the normal standard. This is to be expected according to the results of Susman (1931) and of Wyeth. But in the pneumonia cases the readings for the acidophilic cells were equally as high. A common factor between these two groups, although not obvious, does exist.

The high readings in the tumor cases can be explained by the presence of a growing neoplasm which gives rise to an increased demand on the anterior pituitary growth hormone. In the pneumonia cases the explanation is of an analogous character. The high reading in this latter group is due probably to the great demand for leucocytes in order to cause the consolidation of the lung. As a direct result the bone marrow is compelled to undergo extensive proliferation, which in turn has given rise to a further demand on the anterior pituitary. Thus, in this group as well, tissue proliferation is the probable cause of the increased acidophilic cell readings in the anterior pituitary.

High readings for the chromophobe cells were common in accident cases. At a glance it would appear with some justification that a separate function for this type of cell existed. The fact remains that these cells are shrunken in appearance; in addition, the cells had lost their secretory granules. Both of these points indicate that the chromophobe cells are really in an exhausted state, probably exhausted acidophilic cells.

In the previous analyses the results showed that the basophilic cells were not associated with any particular age, sex, or disease group; nor was there any evidence that the basophilic cells gave rise to any particular secretion. A further point of great importance is that transitional cells of all types were not uncommon, a fact which would not be likely if each type of cell were a separate entity.

Thus the interpretations throughout center about the acidophilic cells and their secretion.

SUMMARY

Detailed examination in a series of 255 unselected cases indicated that the three types of cells present in the anterior pituitary are phases of the one type. In addition the foregoing data disclosed that the pituitary responds to the demands of general diseases in either of two ways. An increased demand for the growth hormone gives rise to an increase in the number of acidophilic cells present. This represents an increase in the normal activity of the gland. There appears to be, as well, an emergency function which comes into play when the individual has been exposed to shock. Then, the acidophilic content of the anterior pituitary is emptied and the cell exhaustion shows itself by an increase in the number of the chromophobe cells present. Thus, the pituitary has a normal function, namely, the control of cell growth, and an emergency function best seen in connection with shock.

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THE RELATION OF LIPIDS TO OESTRIN AND PROGESTIN IN THE CORPUS LUTEUM OF THE SOW

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Evidence obtained in the last few years indicates that the sex hormones may be allied chemically and physiologically to lipids, particularly to cholesterol which, it would appear, may very well in time be found to be the mother substance of these important chemical messengers of the body. The method of preparing progestin as developed by Allen (1) might well be taken for a method to separate some lipid. Butenandt (6) has recently suggested formulas for oestrin and androsterone which bear many points of resemblance to the latest formula deduced for cholesterol by Windaus (10).

The lipid composition of the ovary and corpus luteum has been found to vary with the sexual cycle. Bloor, Okey and Corner (2) have presented the most complete data available in this respect with reference to the corpus luteum of the sow. Boyd (5) has shown that a similar relationship holds for the ovary of pregnant and pseudopregnant rabbits. Preliminary experiments in this laboratory by Elden (8) have shown that the oestrin and progestin content of the corpus luteum of the sow also vary with the sexual cycle. Hence it appeared that a study correlating lipid composition with oestrin and progestin content might throw further light on the probable relationship between these substances. The corpus luteum of the sow was selected for this purpose.

METHOD

Ovaries of sows were collected at the slaughter house as soon as possible after the animals had been killed and not later than on the same day. They were brought to the laboratory, the corpora lutea carefully dissected out and sorted into groups according to age which was judged by appearance and later checked histologically. Lot I was composed of recently ruptured corpora lutea, Lots II to V of variations in age between the 4th and 18th days after rupture and Lot VI of corpora albicanta.

The glands were weighed, ground finely and placed in reservoir bottles containing alcohol. As further material was obtained from the abattoir it was similarly treated and added to the proper container. It required some 10 weeks to get enough material for the purposes of this and associated investigations. At the end of this time, the glandular material was removed from each container and separately extracted with hot alcohol in Bloor percolator-extractors for 12 hours. The several alcoholic extracts from the same lot were combined and added to the alcohol in which the

material had been stored. The total volume of the combined extracts in conjunction with the weight of tissue extracted gave the dilution which varied between 1 in 5 and 1 in 10. Aliquots of the alcoholic extract of each lot were removed for lipid analysis and the remainder used for the isolation and estimation of the hormones present. The determinations of oestrin and progestin were made by methods previously discussed (Elden, 8), while lipid analyses were performed by Bloor oxidative micro-methods as modified by Boyd (3, 4).

Follicular fluid was also analyzed. It was secured free of blood by puncturing the small fluid-containing sacs of the ovaries with a fine syringe and drawing off the contents. Insufficient follicular fluid was obtained to allow estimation of the progestin content (if any) but it was found to contain 165 rat units of oestrin per 100 cc. The total lipid content was 78 mg. per 100 cc. made up of 59 mg. per cent neutral fat, 5 mg. per cent of free cholesterol, no cholesterol esters and 14 mg. per cent of phospholipids. Parhon (9) reported that bovine follicular fluid contained from 55 to 105 mg. per cent of total cholesterol.

DISCUSSION OF RESULTS

The results of the lipid analyses were analogous to those obtained by Bloor, Okey, and Corner (2). Thus, the total fat content of the corpus luteum increased from the time of rupture to reach a maximum between the 9th and 18th days after rupture when it composed 3 to 3.5 per cent of the weight of the gland, after which the percentage of lipids declined. The increase was found to be due chiefly to an increase in phospholipid which rose from 1280 mg. per cent to 2430 to 2600 mg. per cent and then fell to 1270 mg. per cent in the corpus albicans. Ester cholesterol varied between 0 and 59 mg. per cent and neutral fat between 342 and 780 mg. per cent, neither values being related in any way to the age of the gland. Free cholesterol increased steadily in value from the time of rupture, when it was 158 mg. per cent, to the albicans stage at which it was 273 mg. per cent.

The oestrin content of the corpus luteum rose from slightly under 3 rat units per 100 gm. shortly after the time of rupture to reach a maximum of 6 units at the 15th to 18th days, after which it declined in value as the gland degenerated. The percentage of progestin showed two peaks, one shortly after the time of rupture of the follicle, when it was over 4 rabbit units per cent, and the second at the 12th to 15th days, when it was over 5 rabbit units.

The results clearly indicate that phospholipid, free cholesterol, oestrin and progestin of the corpus luteum vary in concentration according to the stage of development of the gland. This relationship has been shown in Figure 1. The degenerating corpus albicans may be concluded to contain reduced amounts of phospholipid and of both hormones. Whether the decrease in phospholipid resulted in the production of less endocrine products or whether it was related to decline in physiological activity generally may not be stated at present. Since the chief physiological func-

tion of the gland appears to be the elaboration of these hormones, the balance of evidence would appear to be in favor of the former view.

The marked increase in phospholipid may be seen to have been accompanied by a lesser rise in oestrin and it may be offered that the latter effect resulted from the former or that both reflect the general increase in activity of the gland. The concentration of hormones could hardly be expected to increase to the same extent as that of the lipids. The hormones are undoubtedly discharged from the gland as rapidly as formed, while there is no evidence that the corpus luteum synthesizes phospholipid for use in other parts of the body.

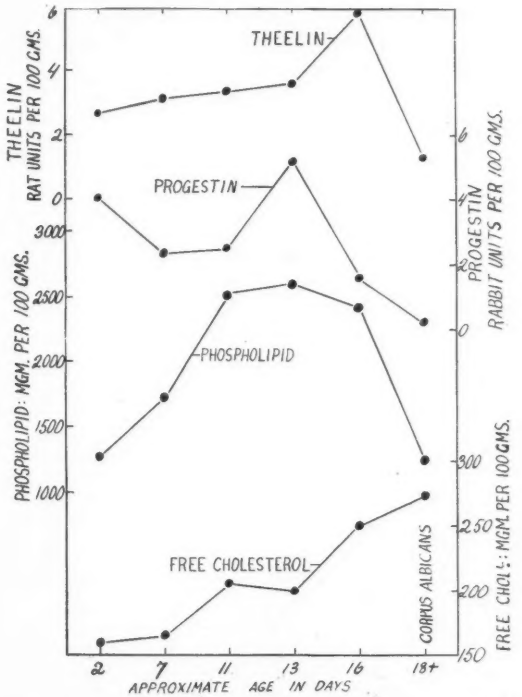

Figure 1. The relation between the concentration of theelin (oestrin), progestin, phospholipid and free cholesterol in the corpus lutum of the sow.

Elden (8) concluded that the concentration of progestin was greatest shortly after the time of rupture. This is practically in line with the older work of Corner (7) who, from histological studies, believed the gland most active up to the 7th day. The observation and the deduction therefrom do not agree with the conclusions based on lipid studies of Bloor, Okey and Corner (2) nor with those herein reported from which the greatest activity would be judged to occur about the 14th day. It is of interest, therefore, that the present study revealed the gland of the 12th to 15th days to con-

tain actually more progestin than at any other time. Elden (8) did not differentiate between glands from the 7th to about the 18th days.

Except for the increase in progestin at the 12th to 15th days, the concentration of this hormone may be seen to have *declined* coincidently with an *increase* in free cholesterol. It may be of significance that free cholesterol in the gland of the 12th to 15th days fell slightly while progestin momentarily rose. These facts suggest an inverse relationship between progestin and free cholesterol.

The value for free cholesterol found shortly after the time of rupture is remarkably low. Boyd (5) found that the whole overy of early pregnancy in rabbits contained about 300 mg. per cent of free cholesterol and that this value increased markedly up to the middle of gestation. May it be that the low value for free cholesterol in the young corpus luteum is due to this substance being used to synthesize progestin? And as the production of progestin falls off with age of the gland, the "normal" level of free cholesterol is gradually attained?

SUMMARY

One hundred pounds of sow corpora lutea were sorted according to age. In each group the percentage of oestrin and progestin was compared with the percentage of total lipids, total fatty acids, total cholesterol, ester cholesterol, free cholesterol, phospholipids and neutral fats.

Changes in the concentration of oestrin were found to be accompanied by corresponding changes in the value of phospholipid; the concentration of progestin varied inversely as that of free cholesterol. Other lipid values were not related to the percentage of the hormones. Follicular fluid contained 165 rat units of oestrin and 78 mg. of total lipids (mostly neutral fats) per 100 cc.

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Abstract Department

Occurrence of an acetylcholine-like substance in the adrenal venous blood on stimulation of the splanchnic nerves (Das Auftreten eines acetylcholinartigen Stoffes im Nevennierenblut bei Reizung der Nervi splanchnici). Feldberg, W. and B. Minz, Arch f. d. ges. Physiol. **233:** 657. 1934.

After injections of physostigmine the venous blood from the adrenal glands collected during stimulation of the splanchnic nerves in dogs and cats acquires the following new properties: contracting action on the eserinized leech muscle, pressor effects on the cat's blood pressure similar to those of a solution containing both acetylcholine and epinephrine. These properties disappear shortly unless the venous blood is eserinized. It is concluded that stimulation of the splanchnics liberates acetylcholine in the adrenal glands.—A. Rosenblueth.

Studies on the adrenal; the relation of the adrenal cortical hormone to the vitamins. Grollman, A. and W. M. Firor, J. Nutrition, **8:** 569. 1934.

No direct interrelationship exists between the adrenal cortical hormone and vitamin deficiencies. The observations of previous workers which appeared to demonstrate the ameliorating effects of the adrenal cortical hormone in avitaminosis B and C are due to the presence of these vitamins (derived from the original glandular material) in crude cortical extracts. Ascorbic acid is less effective by mouth than by parenteral administration. It has no life prolonging effects in adrenal insufficiency.—Authors' Abst., Wistar Bib. Service.

The chemistry of the suprarenal medulla (Zur Chemie des Nebennierenmarks). Huszák, St., Ztschr. f. physiol. Chem. **222:** 229. 1933. Abst., Chem. Absts. **28:** 2035.

The presence of ascorbic acid in the suprarenal medulla has been previously overlooked because the chloroform extract failed to reduce silver nitrate. The reduction of iodine and dibromophenol-indophenol was attributed to some other reducing substance. It is now shown by tests on guinea pigs that the suprarenal medulla of steers does contain ascorbic acid. The failure of the extract to reduce silver nitrate is due to inhibitory substances which may be removed by lead acetate. Similar inhibitory substances occur also in plants, since the silver reduction of lemon and paprika juice can be intensified by a preliminary treatment with lead acetate. Their function is probably a stabilizing of the vitamin.

Chemical studies of the suprarenal gland. Kendall, E. C., J. Biol. Chem. **97:** IV. 1932.

A derivative of epinephrine containing lactic acid may be obtained from an acetone extract of frozen suprarenal gland tissue. Sodium bicarbonate is added to the acetone extract, the solution is extracted with ether, and the derivative may be extracted from the ether with water. It is probable that the derivative is lactyl epinephrine and that epinephrine is retained in the gland in this form. The lactyl derivative has been prepared synthetically from methyl lactate and epinephrine. Both the natural product and the synthetic product have a marked effect in restoring a dog in prostration after suprarenalectomy, but they cannot prolong life indefinitely. Injection of the compound does not cause blanching of the mucous membrane or the response characteristic of epinephrine. It is possible that this derivative is involved as an intermediate compound in the liberation of sympathin. No method has been found to liberate the epinephrine from the derivative by hydrolysis, which suggests that in the organism, the epinephrine is liberated by oxidation of the derivative rather than by hydrolysis.—L. C. W.

Hyperadrenalinemia and its treatment with atropin (Hyperadrenalinämie bei essentieller Hypertonie und ihre Behandlung durch Atropin). Kuré, K., T. Nakaya, S. Murakami and S. Okinaka, Klin. Wchnschr. **12:** 454. 1933.

Previous workers failed to estimate correctly the concentration of adrenalin in the blood, because adrenalin is so readily destroyed by oxygen in alkaline or neutral media. Using both arterial and venous blood obtained with the

ordinary technic in 10 cases, no vasoconstriction could be observed on the Laewen-Trendelenburg frogleg or on the Krawkow-Pissemski rabbit-ear preparation, although both test objects are sensitive enough to demonstrate the constrictor effects of adrenalin up to a dilution of 1:10 millions. If the blood, however, was withdrawn from the artery under precautions excluding contact of the blood with air, vasoconstriction corresponding to an adrenalin concentration of 1:2 millions could be observed seven times in ten cases. The technic described by the authors includes the addition of 1/1000 normal HCl to the blood until its pH is 6.8. Venous blood similarly obtained and prepared does not reveal vasoconstrictor effects. The identity of the vasoconstrictor substance with adrenalin is claimed on the following grounds: (1) The substance is readily destroyed by contact with oxygen; (2) the destruction occurs more rapidly at an alkaline pH and is forestalled by changing the pH to 5 or less; (3) sensitization of the test object with gynergen prevents vasoconstriction. Thus the blood behaves in all three respects like a solution of adrenalin. Applying the same technic to 14 cases of hypertension, vasoconstriction was noted in every case, corresponding to adrenalin concentrations varying from 1:600,000 to 1:1,200,000. Previous work by Kure, Wada and Okinaka seemed to prove that discharge of adrenalin from the adrenals is promoted by stimulation of the spinal parasympathetic. As atropin is known to inhibit the response of organs with spinal parasympathetic innervation, the use of atropin in hypertension seemed to be indicated. Ninety-five ambulatory patients were treated by oral administration of 0.2 mg. atropin sulfate t.i.d., three hours after meals. Blood pressure readings were taken daily at the same hour under well-controlled conditions. Sixty-four of these patients showed a drop of blood pressure within 3 to 10 days. The drop was only 11 to 15 mm. mercury in 10 cases, 16 to 30 in 25 cases and from 30 to 50 in 29 cases. The response to atropin therapy was different according to the type of hypertension. In essential hypertension marked decrease was obtained in 20 of 22 cases (90%), while in the presence of primary contracted kidneys 34 of 43 cases, i.e., 80%, showed comparable good results. In chronic glomerulo-nephritis decrease of blood pressure obtained only in 4 of 19 cases (21%) and the treatment had no effects upon blood pressure in hypertension combined with cardiac disease. The adrenalin content of the blood was determined in 6 cases before and after atropin treatment and in each case a decrease in adrenalin concentration became noticeable. Atropin has been continuously administered to many patients for several months without untoward by-effects. The blood pressure seemed to stay at a lower level for quite some time even after the treatment had been discontinued. Atropin therapy has been successfully combined also with other dietetic and medicinal procedures in the care of hospitalized patients.

—M. A. Goldzieher.

Peripheral circulation during experimental fever. Pinkston, J. O., Am. Physiol. **110:** 482. 1934.

Ear temperature, measured by means of thermocouples and galvanometer, was employed as an indicator of changes in peripheral circulation during experimental fever (typhoid-paratyphoid vaccine) in unanesthetized rabbits. One group of animals (controls—9 in number) had undergone sympathectomy of one ear; another group (5 animals), sympathectomy of one ear, plus inactivation of the adrenals. The onset of fever was characterized by prompt and marked constriction of the normally innervated vessels in all controls; the sympathectomized vessels showed constriction in only about 50% of the controls. Constriction in the sympathectomized ear occurred very promptly in 3 animals, but was much delayed in 2 others. Adrenal inactivation abolished the early constriction, but did not appear to alter the delayed constriction. During the decrease of body temperature at the termination of the febrile response, the sympathectomized vessels did not dilate so completely as did those of the normal ear.—Author's Abst.

Microscopic observations of structural changes in the adrenal gland of the living frog under experimental conditions. Singer, E. and R. L. Zwemer, Anat. Rec. **60:** 183. 1934.

The adrenal glands of 54 living frogs were studied by reflected white and fluorescent light. In white light the normal adrenal gland appears yellow. Indefinitely defined, multi-angular cells are filled with fine granules of uniform size. Round, grayish nuclei are occasionally visible. In 1 hour the contents of some of the cells change from granules to large luminous globules which gradually increase in size and seem to obscure the nuclei and cell boundaries. The appearance of these globules is not associated with injections, exposure to light,

or blood circulation. Ultraviolet light used after injection of aesculine shows a network of fine fibers when white light reveals granular formation, and brown clumps when the globular condition prevails. Pithing, curare and bichloride of mercury induce changes in adrenal cell structure which are apparently due to a diminution of their lipoid content.—Authors' Abst., Wistar Bib. Service.

A study of the blood volume of adrenalectomized dogs. Swingle, W. W., H. M. Vars and W. M. Parkins, Am. J. Physiol. **109:** 488. 1934.

The hemoconcentration of adrenal insufficiency is due to depletion of the blood and plasma volume. It is not merely a terminal event but is one of the primary and initiating factors in the syndrome. Studies of base and chloride changes were not made. The plasma volume of 15 adrenalectomized dogs (16 experiments) was studied, using the dye (Congo red) method. Following withdrawal of cortical hormone, the plasma volume declines with increases in hemoglobin, cells by hematocrit and blood urea nitrogen. After hormone injections the plasma volume rises and the hemoconcentration disappears. Clinical improvement of the animal parallels the increase in plasma volume and decrease in blood concentration. The plasma volume of the 15 animals in insufficiency decreased from 13 to 56%, with an average of 33%. Terminal plasma volume figures ranged from 20 to 46% with an average decrease of 36%. The greatest plasma volume changes were observed in a series of 6 dogs with low initial hemoglobin that had been adrenalectomized 4 to 12 months previously and brought into insufficiency by gradual reduction of hormone dosage over periods of 4 to 8 weeks. The average plasma volume decrease in this group was 39%, with a range of 25 to 56%. The blood volume (total red cell volume) of a series of 10 adrenalectomized dogs was studied by the Welcker (washout) technique. The animals were used for the experiments when the blood pressure stood at various levels. The average whole blood volume of 4 normal dogs was 80.4 cc. per kg.; the average for 4 adrenalectomized dogs off extract and free from evident symptoms, with blood pressures varying in the different cases from 86 to 80 mm. Hg. was 53.2 cc. per kg., the average for 6 dogs off extract with blood pressures varying from 75 to 42 mm. Hg. was 33.3 cc. per kg., the average for all 10 adrenalectomized animals was 43.2 cc. per kg., representing 46.2% decrease from normal. The average amount of free bleeding of 4 normal dogs was 59.2 cc. per kg., for 4 adrenalectomized animals off extract, but free from clinical symptoms, and with blood pressures ranging from 85 to 80 mm. Hg. 25.9 cc. per kg.; for 6 adrenalectomized dogs off extract with blood pressures ranging from 75 to 46 mm. Hg. 23.1 cc. per kg.; the average "free bleeding" volume for the series of 10 adrenalectomized dogs being 24.5 cc. per kg., representing a 58.6% decrease from normal. Both the dye and Welcker methods of blood volume determination do not appear to be entirely satisfactory when employed in conditions such as adrenal insufficiency, in which marked stagnation, and collapse of large areas of the circulation, and shunting of blood, occur.—Authors' Summary.

The effects of active substances of the suprarenal cortex and of adrenaline on the contractions of muscle or normal and suprarenalectomized frogs (Der Einfluss von Wirksubstanzen der Nebennierenrinde und von Adrenalin auf die Leistungen der Muskeln normaler und nebenniereloser Frösche). Wachholder, K. and V. Morgenstern, Arch. f. d. ges. Physiol. **232:** 444. 1933.

Excised muscles from normal and from suprarenalectomized frogs (3 animals 2-3 days after operation, 14 animals 3-4 days after operation) were placed in baths of oxygenated Ringer's solution, and the effects of various extracts on their contraction were studied. The cortical hormone B of Schmitz and Kühnau in concentrations of 0.02 to 0.2 mg. per cent had a direct fatigue-lessening influence on the muscles of normal frogs. This effect was much more important in the case of suprarenalectomized animals, in that the easy fatigability of the muscle was for the greater part eliminated. To produce this effect stronger concentrations (about 1 mg. per cent) were required. The cortical substance A of Schmitz and Kühnau had a similar but much weaker effect. Eucortone (cortical extract of Swingle) had no demonstrable effect on the contractibility of the muscles of normal frogs. In suprarenalectomized frogs some improvement of contractions occurred with strong concentrations, but not regularly. Adrenaline in a dilution of 1:500,000 had a slight beneficial effect on contraction, but stronger or weaker concentrations hastened fatigue. This effect was the same on the muscles of normal and of suprarenalectomized frogs.

—L. C. W.

A study of the seasonal changes in the adrenal gland of the thirteen-lined ground-squirrel (Citellus tridecemlineatus), with particular reference to its sexual cycle. Zalesky, M., Anat. Rec. **60**: 291. 1934.

A definite interrelationship is shown to exist in the thirteen-lined ground-squirrel between the adrenal cortex and the reproductive cycle. Thus, a significant increase in adrenal size and weight traceable to cortical hypertrophy takes place in the adrenal of both males and females during the breeding period or as a result of artificial stimulation of the gonads and reproductive accessories at the season of sexual inactivity. Histologically, this cortical hypertrophy is associated mainly with the expansion of the reticular zone and the differentiation, within it, of a characteristic, highly developed outer sub-zone termed "reticularis A" and described fully in the paper. Castration of at least 1 month's duration leads, in the adrenal of either sex, to degenerative changes in the zona reticularis.—Author's Abst., Wistar Bib. Service.

Suprarenocortical syndrome and pituitary basophilism; unusual case of hirsutism and alopecia. Bannick, E. G., M. Clin. North America, **18**: 411. 1934.

The first case is that of pluriglandular dysfunction presenting in many respects the classical picture of Cushing's pituitary basophilism with a few additional features. A woman was treated in July, 1930, for attacks of epilepsy of a year's duration. In February, 1933, she reappeared for attention to hirsutism of the face, thorax and abdomen, arterial hypertension, obesity especially of the abdomen and upper part of the extremities, and weakness, menstrual irregularity and some osteoporosis of the skull. Roentgen examinations revealed a large renal shadow on the left. The sella turcica and the visual fields were normal. The epileptic seizures were still present but less severe. The basal metabolic rate was minus 7% and blood chemistry revealed nothing abnormal. Exploration of the suprarenal area was suggested, but the patient refused operation. The second case occurred in a woman whose chief complaint was a combination of hirsutism and alopecia. The hair was particularly marked over the legs and arms, less so over the abdomen and thorax. There was alopecia of the scalp starting in the frontal area which was gradually increasing. Thyroid substance and injections of pituitary extract did not improve the condition. Aside from moderate arterial hypertension, the history and physical examination gave normal findings.—I. B.

Endocrinology; a present-day summary. Denison, R., Pennsylvania M. J. **38**: 313. 1935.

This is an excellent though brief review of the present-day knowledge of the subject as it applies to the general practitioner. The hormones of the ovary, pituitary, thyroid, parathyroid and adrenal glands are discussed from a clinical viewpoint, and the known functions of these organs are well tabulated.
—I. B.

A study of the relationship of internal secretions to the metabolism of malignant tumor tissue. Meyer, O. O. and Claire McTiernan, Am. J. Cancer, **20**: 96. 1934.

Using the method of Warburg for the study of tissue microrespiration, the authors studied the effect of the various hormones upon the metabolism of transplanted mouse tumors, chiefly Sarcoma No. 180. Insulin, prolan extracts of suprarenal cortex, thymus extract, theelin and thyroxin were administered to different groups of mice bearing tumors, for varying periods of time. Then the animals were killed and simultaneous with the measurement of the respiratory and glycolytic activity of the tumor, the metabolism of the liver tissue of each animal was determined and this served as a control for the tumor tissue. Untreated tumor bearing animals were used as controls for the treated. The results of the above procedures are reported. Most striking of these was the depressing effect of thyroxin upon the tumor oxygen consumption associated with simultaneous rather marked stimulation of the liver oxygen consumption. Appreciable inhibition of the oxygen consumption for tumors (sarcoma No. 180 and carcinoma No. 63) was noted in a distinct majority of the experiments. In none of the experiments was the respiration of the tumor stimulated. The results after thyroidectomy were not distinct. The results after orchidectomy were suggestive for a decrease in tumor oxygen consumption, but not conclusive. The results after suprarenalectomy were equivocal. Insulin affected distinctly only the tumor glycolysis by producing a reduction. The other hormones, though affecting the liver in some instances, did not affect the metab-

olism of the transplanted tumor. The paradoxical effect of thyroxin upon tumor metabolism was not explainable. Apparently it was dependent upon some unusual factor within the tumor tissue itself. Microscopically, the tumors of the controls and the thyroxin-treated mice were indistinguishable.
—O. O. Meyer.

The existence of antiblastogenic substances in the suprarenal and hypophysis (Au sujet de l'existence de substances antiblastiques dans la surrénale et l'hypophyse). Vassiliadis, H., Compt. rend. Soc. de biol. **115:** 1241. 1934.

Ether extracts of the adrenal glands and hypophyses of normal mice injected intraperitoneally into tar-treated animals (number not stated) materially inhibited cancerous growths. The antiblastogenic substances are not restricted to the suprarenals and hypophysis, their presence having been previously determined in other organs.—J. C. D.

A study of certain endocrine effects on the mammary glands of female rats. Weichert, C. K., R. W. Boyd and R. S. Cohen, Anat. Rec. **61:** 21. 1934.

A series of experiments is reported in which various endocrine factors were studied with regard to their effect upon the mammary glands of rats. The results of feeding of daily doses of 0.5 gm. desiccated thyroid gland to castrated and normal rats were compared with those obtained by administration of certain ovarian, pituitary and pituitary-like hormones. Mammary glands of ovariectomized female rats fed thyroid showed no development beyond the branching duct stage. Normal rats similarly treated showed greatly stimulated mammary glands, well vacuolized and with abundant secretion. Such stimulation occurred, however, only during the pseudopregnant period induced by the experimental hyperthyroidism. Furthermore, the type of development in these stimulated glands was unusual in that characteristic lobule formation was not generally apparent. Perhaps the reduction of adipose tissue in the region of the mammary gland may explain this variation. A study of the development of the mammary gland during the pseudopregnant period induced by copulation with a vasectomized male, contrary to the reports of some investigators, showed that the gland at the end of the pseudopregnant period is not strictly comparable to that of a pregnant animal at a corresponding period of pregnancy. Instead, it more closely resembles the gland of a pregnant animal just before parturition.—Authors' Abst., Wistar Bib. Service.

Endometrial findings in functional menstrual disorders. Anspach, B. M. and J. Hoffman, Am. J. Obst. & Gynec. **28:** 473. 1934.

In a study of 96 cases of amenorrhea, 97 cases of uterine bleeding and 42 cases of apparently normal menstruation treated for dysmenorrhea, sterility, and obesity, the authors found no constant relationship between the clinical symptoms and the development of a premenstrual endometrium. While the development of a premenstrual endometrium invariably coincides with ovulation and the development of a corpus luteum and our understanding of the anabolic cycle is complete, amenorrhea, uterine bleeding and what appears to be normal menstruation is associated with so many different states of the ovary that we cannot from our present knowledge understand the catabolic cycle. The authors' clinical and laboratory findings seem to endorse the recent tendency in the literature to question: (a) the constance of the relationship between the state of ovarian function and the periodicity of the flow; (b) the truth of the idea that most healthy women menstruate regularly and at 28-day intervals; (c) the validity of the view that menstrual bleeding depends upon a regression of the corpus luteum (negative phenomenon). It is believed that bleeding may be due to some positive mechanism, thus far unexplained. As amenorrhea, oligomenorrhea and functional uterine bleeding of any sort are unreliable as positive indices of ovarian function, test curettage is important as a diagnostic procedure in the diagnosis and treatment of functional gynecologic disorders. A correct evaluation of the uterine mucosa depends upon the recovery of mucosa from all parts of the uterine cavity. The use of a pipette curette seems inadequate for this purpose.—Authors' Summary.

Glandular physiology and therapy; pregnancy tests. Aschheim, S., J. A. M. A. **104:** 1324. 1935. Abst. A. M. A.

The author states that no hormones are known that appear solely and constantly during pregnancy; there are no specific hormones of pregnancy. Con-

sequently there is no specific hormone pregnancy reaction in the strict sense of the word. In human pregnancy there occurs so great an increase of certain hormones in the blood and so large an excretion of these hormones in the urine that, on the basis of this increased production and excretion, it is possible to diagnose pregnancy with the aid of animal experiments. The basis of the biologic pregnancy test therefore lies in quantitative and not in qualitative hormonic differentiation of the blood or urine of the pregnant woman as contrasted with the blood or urine of the nonpregnant woman. This difference is so exceptionally great that it may be considered the outstanding characteristic of the blood and urine in pregnancy. There are two types of hormones that are definitely increased during pregnancy: 1. The estrus-producing hormone, which may be demonstrated by the Allen-Doisy test in the castrated mouse or rat. 2. The gonadotropic hormone, which is similar in its effects to the gonad-stimulating substance of the anterior lobe of the pituitary; this principle may be demonstrated (a) by the changes in the ovaries that result from its administration to the infantile mouse or rat, (b) by its effects on the endocrine function of the testicles of the infantile mouse or rat, or (c) by the changes produced in the ovaries of the mature rabbit. The discussion presented by the author is intended to acquaint the practitioner with the nature and reliability of the hormone pregnancy reaction so that he may make use of it in conjunction with clinical observations in the diagnosis of pregnancy.

Amount of folliculin in the body fluids of a woman castrated in the second month of pregnancy (Dosage de la folliculine dans les humeurs d'une femme castrée au deuxième mois de sa grossesse). Brindeau, A., H. Hinglais and M. Hinglais, Compt. rend. Soc. de biol. **115:** 1509. 1934.

Quantitative tests for folliculin were made on a woman close to term. Her right ovary had been extirpated a year previously, and her left ovary removed in the second month of pregnancy. The amount of folliculin in the blood, urine, and placenta was found to be that which would be expected under normal conditions. The authors state that these results indicate an extra-ovarian (probably placental) origin of folliculin.—J. C. D.

The gonad-stimulating hormone of pregnant mares. Catchpole, H. R. and W. R. Lyons, Am. J. Anat. **55:** 167. 1934.

The distribution of gonad-stimulating hormones has been studied in about 70 mares sacrificed at various stages of pregnancy. Hormone was found in blood, chorion, endometrium, hypophysis, and to a lesser degree in other tissues, in amounts varying according to time of pregnancy in an interesting and significant manner. Hormone was found in maternal hypophysis in the earliest stages studied; in chorion as early as the 1.8-cm. fetal crown-rump length; and in blood and endometrium as early as 2.0 cm. It was detected in these tissues until about the 35.0-cm. stage. Thereafter it was present minimally, or absent. Quantitative figures on the hormonal distribution in the tissues studied lend poor support to the simple theory of its hypophyseal origin. They may be used, however, as the most potent argument yet offered for a chorionic production of this hormone, without, it must be admitted, closing the issue. An histological study has been made of placental sites at those stages of pregnancy critical as to hormonal distribution. The relation of the hormone to the maternal and fetal gonads has been discussed. Comparisons have been instituted between the present results and the general body of data concerning gonad-stimulating hormone in pregnancy in other forms, and in various pathological and experimental conditions.—Authors' Abst., Wistar Bib. Service.

The distribution and source of oestrin in the pregnant mare. Catchpole, H. R. and H. H. Cole, Anat. Rec. **59:** 335. 1934.

A quantitative study has been made of the distribution of oestrin in the tissues of four mares and their respective fetuses. Hormone has been found in mare kidney, endometrium, and ovary; in fetal gonads, liver and kidney; in the allantochorion, both during pregnancy and at term. The amounts of oestrin in the urines of mares antepartum and postpartum have been determined as have also the amounts of oestrin in the urines of new born foals. It was found that there is a gradual fall in the oestrin content of the urine during the last 2 months of pregnancy. One day antepartum appreciable amounts of oestrin are present but oestrin was not found in the postpartum urines. The first voided urine of the new-born foal contained oestrin, but subsequent sam-

ples did not. These findings are discussed in relation to the morphological changes occurring in the fetal and maternal gonads over the period studied. It is concluded that the theory of placental formation of hormone must be adopted in this form.—Authors' Abstract.

Changes in vaginal epithelium during pregnancy in relation to vaginal cycle. Davis, M. E. and C. G. Hartman, J. A. M. A. **104:** 279. 1935. Abst., A. M. A.

The authors studied the cyclic changes in the vaginal epithelium in a large group of female monkeys by means of frequent biopsies. These rhythmic changes were coordinated with ovarian activity and ovulation. They found that the epithelium attains its greatest thickness in the midinterval, consisting at this time of an active basal layer, an inactive functional layer, and an intra-epithelial zone of cornification interposed between these two, which they call Dierks' layer. Following ovulation, desquamation begins and proceeds by a crumbling away of the functionalis, which is usually not completely destroyed. Mitosis begins in the basalis on the first day of menstruation, becoming most marked near the time of ovulation, and then gradually subsides. A cessation of ovarian activity, such as is seen at the menopause or an abnormal ovarian activity definitely alters these physiologic changes. Early in pregnancy the epithelium remains in the same state as is seen during ovulation, consisting of the typical three layers. Desquamation of the functional layer continues throughout pregnancy but is increased progressively following the middle of pregnancy. At the end of pregnancy only the basalis remains and is of irregular thickness, in many places of only three or four cells. In the postpartum period the epithelium is rapidly restored to normal at the end of the first month. Hormone influences are probably responsible for these phenomenal changes. The human female, as well as the monkey, exhibits the described cyclic activity of the vaginal mucosa as well as the changes during pregnancy.

Analysis of errors inherent in pregnancy tests based on the Aschheim-Zondek reaction. Davy, L. and E. L. Sevringhaus, Am. J. Obst. & Gynec. **28:** 888. 1934.

In 425 cases tested for pregnancy by methods based on the Aschheim-Zondek reaction, a total accuracy of slightly more than 90% of the series was attained. Three modifications were employed either as individual methods or as concurrent tests with interpretation of the results as a single test. Analysis of the data reveals that erroneous diagnoses, due to limitations inherent in pregnancy testing by these methods, were made in 8% of the cases. Such systematic errors occurred in 3.92% of the pregnancies. Two were in very early pregnancies testing correctly positive later. In early pregnancies, more consistently accurate results were obtained by a modification of the Friedman rabbit test or by an immature female rat test than by the Schneider immature rabbit method. Incorrect negatives were obtained in 9 pregnancies of more than one month duration. In 7 of these there was definite fetal or maternal pathology; in one there was no known pathology; and in one the history was not reliable. Faulty tests obtained in 12.7% of the non-pregnant group may be classed as systematic errors. Many of the cases which gave false positive tests can be correlated with known gynecological problems in which there was demonstrable endocrine disturbance. Each of the cases testing incorrectly positive has been studied from the standpoint of the clinical features manifest before and after the test and with respect to the ovarian picture obtained in the injected animals. Correlation of the laboratory and clinical findings suggests that cases of ovarian dysfunction in the non-pregnancy can be differentiated from pregnancy by the concurrent application of 2 or more tests to the urine. In cases of this type, false positives have not occurred with the use of either the Schneider immature rabbit or the immature female rats as test animals. The more highly sensitive Friedman rabbit is of value for the demonstration of gonad-stimulating substance in the urines of non-pregnant individuals.—Authors' Summary.

Reaction of the mature human ovary to antuitrin S. Geist, S. H., Am. J. Obst. & Gynec. **26:** 588. 1933.

In 50 cases, in women between the ages of 33 and 48, varying doses of antuitrin-S, from 600 rat units to 2200 rat units, given over a period varying from 36 to 100 hours, resulted in definite changes in the ovaries. The injections were given subcutaneously, as much as 600 units being given in one day

in divided doses. In 33 cases the changes to be described were found. In a control series of 25 noninjected cases the ovaries in 4 showed changes comparable to those found in the injected cases. The ovaries of the injected patients were obtained at operation, usually performed for uncomplicated fibroids. They presented a marked congestion of the vessels of the hilus with occasional extravasations into the hilus, probably due to rupture of small vessels or diapedesis. In the stroma, likewise, there was a marked increase in the vascularity and not infrequently haemorrhagic extrasation. Apparently there was no stimulation of the follicle; rather an arrest of follicular development. The impression derived is that the follicles ceased to develop beyond the point that they had reached at the time of the injection. The number of cystic follicles seemed increased. They were from 2 to 20 mm. in diameter. The wall was smooth or thrown into small folds; the lining glistening or dark and pigmented. A characteristic finding about these cystic follicles was the presence of hemorrhage; in some cases this perifollicular haemorrage had extended into the cavity of the follicle. The theca lutein cells in many instances were prominent and increased in number. Occasionally a corpus luteum was found with massive haemorrhage into it. The intensity of the reaction in the ovary seemed to bear a direct relationship to the amount of hormone injected. The subjects that were injected over a period of 96 hours or more seemed to be most affected. The findings that have been described suggest that the substance exhibited has a definite effect on the human ovary.—Author's Abst.

Recovery of testicles injured by menformon, spontaneously or through action of gonadotropic hormones. de Jongh, S. E. and E. Laqueur, Nederl. tijdschr. v. geneesk. **78:** 3030. 1934. Abst., J. A. M. A. **103:** 536.

de Jongh and Laqueur state that the size of the testicle is no measure of its endocrine activity. Testicles of young animals treated with the gonadotropic hormone complex from the urine of pregnant women, by which treatment their hormone production is selectively stimulated, are hardly or not larger than those of untreated controls. The power of the gonadotropic hormone complex to cause a discrete growth becomes evident in testicles that are artificially made to regress by treatment with estrin. In this case their weight is restored more completely by the gonadotropic hormone complex than without it. Far greater is the influence of the gonadotropic hormone complex on the development of Leydig's tissue of the testicle and on the size of the other male organs measured in this case by the seminal vesicle.

New biologic test for hormones in pregnancy urine. Kanter, A. E., C. P. Bauer and A. H. Klawans, J. A. M. A. **103:** 2026. 1934. Abst., A. M. A.

The authors place a previously standardized fish in a two-quart bowl containing 1 quart of water at about 75 F. The fish is observed to make certain that the oviduct is not beyond normal limits. Four cc. of the urine to be tested is put into this water. The fish is observed at intervals of 24 hours. If the test is found to be positive after the first 24 hours the test is discontinued; if negative, it must be carried out for 72 hours before a definitely negative report may be given, in spite of the fact that about 80% of the positives were positive at the end of the first 24 hours. Normally the oviduct is about 2 mm. in length and reaches less than half the distance to the end of the ventral fin. With a positive reaction the ovipositor reaches past the edge of the ventral fin or to a length of 15 to 25 mm. After the test is completed the fish is put into a tank for recovery and left for from two to three weeks in order to allow for the regression following the positive reaction. It may then be used for other tests. At the outset the authors deemed it advisable to run the fish tests parallel to Friedman tests in order to determine the relative merits of the two. To date they have 31 such tests, with 27 absolute checks and 4 discrepancies between the two tests. Tests were also made on 5 ectopic pregnancies, proved at operation, which were all positive but which had not been checked against the Friedman test.

Investigation of new biologic test for hormones in pregnancy urine. Kleiner, I. S., A. I. Weisman and H. Borowsky, J. A. M. A. **104:** 1318. 1935. Abst., A. M. A.

The authors employed the new biologic test for hormones in pregnancy urine, used in experiments by Kanter, Bauer and Klawans, who intimate the usefulness of the female bitterling in the diagnosis of pregnancy. They used

the lengthening of the female ovipositor as a criterion of positive reaction for the hormones of pregnancy urine and suggested a method of standardizing the female bitterling. Only 9 of the authors' 21 urines from pregnant women gave definitely positive reactions. Of 7 from normally menstruating nonpregnant women, 4 gave positive reactions. One male urine of the 4 tested was positive, and a later specimen from the same male gave positive reactions in every one of the 6 fish tested. Urines from women who had passed the menopause were positive in 1 of 3 cases. Boiled urines from pregnant women were positive in some instances and negative in others. These results agree with those of Szusz and indicate that this biologic reaction is not a specific test for pregnancy as Kanter, Bauer and Klawans intimate. Moreover, the latter investigators do not report as great a variety of controls as the authors have and as Szusz previously reported. The observations that nonpregnant female urines, postmenopausal urines, male urines, boiled pregnancy urines and physical disturbance may bring about lengthening of the ovipositor would seem to show that a standardization of a fish, as suggested, would be extremely difficult if not impossible. Whether the phenomenon is due to the presence of estrogenic substance or to some other hormone or to some other substance remains to be determined.

Action of folliculin on the fecundity of male rabbits (Action de la folliculine sur la fécondité du lapin mâle). Lacassagne, A., Compt. rend. Soc. de biol. **115:** 579. 1934.

Three male rabbits (9, 10 and 18 months old) were given different dosages of folliculin by injection. Large dosages caused testicular atrophy and arrest of spermatogenesis. Spermatogonia were not affected and resumed their activity when the injection treatments were suspended.—J. C. D.

Action of folliculin on the development of the genital organs of male rabbits (Action de la folliculine sur le développement des organes génitaux du lapin mâle). Lacassagne, A., Compt. rend. Soc. de biol. **116:** 95. 1934.

One male and 6 female rabbits of a litter were injected with varying doses of folliculin. The injections began the day the animals were born and lasted for 2 months. Development and sexual maturity of the females were not affected. At the age of 7½ months the male rabbit was killed and autopsied. A histological study of the reproductive organs indicated that the external genitalia and the testis had been arrested in development. There was no inhibition of growth of the ducts of the epididymis or vas deferens.—J. C. D.

Note on a cause of mammary adeno-carcinoma; study on folliculin in colostrum (A propos d'une pathogénie d l'adéno-carcinome mammaire: recherche de la folliculine dans le colostrum). Lacassagne, A. and W. Nyka, Compt. rend. Soc. de biol. **116:** 844. 1934.

Colostrum obtained from pregnantwomen (number not stated) and injected into spayed mice (number not stated) provoked a characteristic estrus. The liquid obtained from cysts near an epithelioma of the mammary gland of a woman likewise induced estrus in spayed mice. It was inferred that folliculin was present in both fluids injected. The authors suggest that folliculin might be a causal factor in the pathogeny of mammary adeno-carcinomas.
—J. C. D.

The follicular apparatus of the ovary of the immature rat and some of the factors which influence it. Lane, C. E., Anat. Rec. **61:** 141. 1934.

The ovaries of 60 normal rats, between the ages of 15 and 66 days were examined histologically and accurate counts made of all follicles possessing at least a two-layered granulosa. If this layer was intact the follicle was classified as "primary." If the granulosa was loosened or actually contained an antrum, it was classified as "vesicular." The average percentage of the total follicles which were vesicular was 11% at 15 days; climbed to 39% at 37 days; fell to 29% at 50 days and then ascended sharply until it reached 50% at ovulation (66 days). The curve of the weight of the ovary paralleled the curve for the percentage of vesicular follicles. The curve of the mean follicular diameter was roughly parallel to that of the vesicular percentage. The follicle-stimulating and the luteinizing hormones were injected into 50 22-days-old rats in various doses, and the ovaries were similarly examined. Administration of the follicle-stimulating hormone increased the total numbers of follicles in the

28-day-old rat by 68%; no effect was demonstrated on the vesicular percentage of this total. Administration of the luteinizing hormone had no significant effect on the total number of follicles contained in the ovary, but increased the vesicular percentage 58%. The mechanism of augmentation is discussed in the light of these observations.—Author's Abst., Wistar Bib. Service.

A study of the effects of theelin on gonorrheal vaginitis in children. Lewis, R. M., Am. J. Obst. & Gynec. **26**: 593. 1933.

Dissatisfied with the results obtained with local applications of antiseptics to the vaginal mucosa in cases of gonococcal vaginitis in children, the author believed it possible that the gonococcus might be eliminated if the thin mucosa of the child could be changed to a thicker structure, or to one of a different type. Eight children with typical gonococcal vaginitis were treated with 50 rat units of theelin hypodermatically every 8 or 12 hours. The first four of these were treated for 10 or 12 days only. The remainder were treated for periods varying from 19 to 98 days. No ill effects were apparent. All 8 cases showed a great thickening of the vaginal mucosa by 20 or 30 superimposed layers of vacuolated cells. Microscopic sections of superficial clippings taken from the vaginal walls resembled the structure found in the premature or newborn child. The children receiving the most theelin showed an hypertrophy and increased vascularity of the vulva resembling that of the newborn female. In one instance a slight hypertrophy of the right breast was noted. No child bled from the vagina during or after treatment. Smears showed a profuse degeneration of epithelial cells. In all 8 cases treatment was continued until vaginal discharge ceased and no Gram-negative intracellular diplococci could be found in a series of smears. The patients were under observation after discharge from the hospital for periods varying from seven weeks to seven months. Three recurrences were noted. Complete involution of the structures affected by the theelin was observed a few weeks after the treatment was ended.—Author's Abst.

An experimental study of ovarian irradiation and transplantation in the rat. Mandel, J., Anat. Rec. **61**: 295. 1935.

Ovarian irradiation of immature albino rats, 7 to 10 days of age, was followed by precocious vaginal opening and the appearance of oestrual changes at approximately 22 days of age. The ovaries at the time of vaginal canalization were characterized by huge follicles with enormous antra. When x-ray dosages of 540 "r" units were applied to the ovarian region of a group of immature animals the ovaries at 6 weeks' post-irradiation possessed many large follicles and the genitalia were normal in appearance. Such ovaries when transplanted into previously castrated immature females induced premature vaginal opening and oestrus. On the other hand, when dosages varying from 830 to 1240 "r" units were employed the ovaries at 6 weeks' post-irradiation were made up mainly of proliferative cords and interstitial tissue together with a few large follicles. The sex accessories of these animals were castrate in appearance. Such ovaries when transplanted into previously castrated immature females were incapable of influencing the time of sexual maturity. The data obtained appear to lend support to the view that, in the rat at least, the follicular apparatus exercises the dual endocrine function of maintaining the sex accessories and of "stimulating" the anterior lobe of the hypophysis.

—Author's Abst., Wistar Bib. Service.

A case of probable superfetation in the cat. Markee, J. E. and J. C. Hinsey, Anat. Rec. **61**: 241. 1935.

A case of probable superfetation in the cat has been described. Two normal kittens were born and 13 days later two more normal ones were delivered. Anatomical evidence is presented which indicates that one uterine horn was occupied by the first two fetuses and the other by the latter two. One uterine horn delivered without producing abortion in the opposite one. The only alternative to the implication that ovulation, fertilization and implantation had occurred during the pregnant state would be that the latter two fetuses had been retained 13 days longer than the first. Histological examination has shown that the right uterine horn, which had delivered first, had undergone involution while the left one continued in pregnancy. This observation indicates that there is some local factor which is necessary for the maintenance of the uterus in the pregnant state in addition to the hormonal ones.

—Authors' Abst., Wistar Bib. Service.

On the humoral exchanges between parabiotic animals; the question of the passage of estrin from normal to castrated animals. (Sur les échanges humoraux entre les animaux en parabiose. La question du passage de l'oestrine des animaux normaux aux chatrés). Martins, T., Compt. rend. Soc. de biol. **115:** 1342. 1934.

In cases (number not stated) of experimentally produced parabiosis between normal and spayed adult female rats, estrus cycles occurred in both rats. It was the author's opinion that the transfer of a substantial quantity of estrin from the normal to the spayed animal depended in particular on suitable vascular communication and perhaps on the condition of the ovary.—J. C. D.

Refractoriness to ovarian stimulation in the rhesus monkey. Meyer, R. K. and E. L. Gustus, Science, **81:** 208. 1935.

Each of 5 immature female rhesus monkeys was injected daily with a highly purified gonad-stimulating hormone prepared from the serum of the pregnant mare. The period of injection varied from 45 to 70 days. Under the influence of the hormone, reddening of the sexual skin and great increase in the size of the follicles was observed. However, these criteria of ovarian stimulation disappeared during the time the hormone was being administered. Menstruation also occurred during this time and following the fading of the sexual skin and decrease in the size of the ovaries. Injection of the serum, obtained from the monkeys at the time the ovaries had regressed, into immature rats together with the gonadotropic hormone completely inhibited the action of the hormone. The amount of serum required for this antagonistic action was relatively very small. Serum obtained from the same monkeys before the injection of the hormone was without antagonistic action when tested in the immature rat. An apparent refractory condition of the ovaries of the immature monkeys was produced by chronic treatment with the purified hormone. This condition is believed to be related to the presence of a substance in the serum which prevents the continued action of the hormone on the ovaries of the monkey.—Authors' Abst.

The testis hormone. Moore, C. R., J. A. M. A. **104:** 1405. 1935. Abst., A. M. A.

The author discusses the biologic functions of utility that the testicle exercises in the organism. He presents some of the general phases and particular details of the testis hormone and discusses some of the principles and possibilities of its clinical application. The experimental animal must be depended on for presenting the various aspects, since knowledge of the manifestations of hormone deficiencies in man, of methods of detecting the presence or absence of the hormone, or of its utility in the species is so limited as to be of little value. It is apparent that the question of the clinical value of testis hormone is by no means settled. For attaining dependable results the problem must be considered from the broad point of view of social background and biologic principles. Real advancement must rest on honest critical work rather than on poorly conceived sporadic experimentation with hastily assumed results and unsubstantial claims. The principal sources of testis hormone are the testicles of large mammals and human urine. Testis hormone is obtained from the lipoid fraction and has been sufficiently purified to yield crystals having a high potency. It appears chemically to be a ketone-alcohol; the only known method of detecting its presence consists in reactions produced in suitable animals. It is secreted continuously, or periodically, in different animals, and secretion is largely under the control of the pituitary gland. It is uncertain whether more than one hormone is secreted by the testis. Its clinical use is questionable; its primary function is the control of the accessory reproductive organs; it is not a testicular stimulant.

On the control of reproductive activity in an annual-breeding mammal (Citellus tridecemlineatus). Moore, C. R., G. F. Simmons, L. J. Wells, M. Zalesky and W. O. Nelson, Anat. Rec. **60:** 279. 1934.

This paper presents the general results from a cooperative study of the reproductive systems in an annual-breeding mammal. The study represents an attempt to gain detailed information of the cycle of each part of the reproductive system of both sexes and to gain information regarding the factors that regulate single yearly cycles. Detailed consideration has been given to the adrenal, thyroid and pituitary and their correlation with the gametogenetic

and endocrine activity of the gonads of both sexes. Accessory reproductive organs respond to injected homologous sex hormone and can be brought into full functional activity at any season of the year. Gonadal activity is stimulated by pituitary tissue, pregnancy urine or their extracts. Anterior pituitaries exert strong gonadotropic action if taken on the approach of or during the active reproductive period but not during the inactive period. Activity is associated with a definite cytological state. Changes in adrenals of normal and treated animals suggest a strong correlation with the reproductive cycle; the thyroid appears to lack this definite correlation and to run an independent cycle. The study suggests that the annual cycle is controlled through pituitary activity and inactivity, which in turn appears to rest upon an internal hormonal factor, and an external environmental factor other than light. Detailed results will appear in separate papers.—Authors' Abst., Wistar Bib. Service.

Action of the female sex hormone on the interstitial cells of the ovary (L'action de la Gynekhormone sur la gland interstitielle de l'ovaire). Parhon-Stefanescu, C., Rev. franç, d'endocrinol. **12:** 225. 1934.

Based on a survey of the literature and his own experiments, the author concludes that a general law may be established that injection of the product of any gland into an organism puts at rest the same organ in that organism. In this regard he cites literature referring to the thyroid, parathyroid, pancreas and ovaries. His experiments consisted of injecting 2 doses (50 units) of progynon per day into two dogs one month old, and into one guinea pig weighing 180 grams 25 units of the same substance were injected twice a day. There were two control dogs and one guinea pig. After 27 days one dog showed increase in volume and congestion of pelvic organs. In the injected animals the ovaries showed a diminution in size and number of interstitial cells. In the control animal there was in each microscopic field an average of 15.1 groups of cells, each group containing an average of 15.1 cells while in the injected animal there was an average of 12.5 cell groups with 3.25 cells per group. After 38 days there was a further diminution — 7.8 groups with 4.9 cells per group. No difference was noted in the Graafian follicles. Similar findings were made in the guinea pig. The experiments are suggestive but inconclusive since only three animals were injected and even the controls showed considerable variation.—J. P. P.

Environment, constitution and menarche (Unwelt, Konstitution und Menarche). Peller, S. and I. Zimmermann, Ztschr. f. Konstitutionslehre, **17:** 258. 1932.

This study is based on 3852 girls. A disproportionately large number of girls begin to menstruate in the month of January. This is apparently not due to climatic or nutritional factors. Daughters of the laboring class do not menstruate as early as those of other classes. Social status has more influence on hastening sexual maturity than on stature. There is greater correlation between body weight and early onset of menstruation than between stature and menstruation within a given social group. In overweight girls the onset of sexual maturity depends on the degree of disproportion between length and weight (Pfaundler's data), although in their own series there was no definite correlation between the ratio of weight to length and the early onset of menstruation, probably because the authors' cases were too mixed as to social economic status—A. T. R.

Artificial menstruation; effect of female sex hormones in amenorrhea. Rock, J., New England J. Med. **210:** 1303. 1934.

The cyclic changes in the endometrium of mature human beings have been described and correlated with synchronous changes in the ovaries. A modification of the Klinger-Burch suction curette has been described and shown to be of service in the study of the endometrium and through this of female sex-endocrine physiology. Seven instances of artificial menstruation in 4 patients have been described. In 3 instances the flow followed injections of folliculin only; in the other 4 folliculin was followed by corporin. When only folliculin was used the flow is shown to have been from endometrium in the proliferating phase. When both were used a true secretory endometrium was generated. The changes in the endometrium were accomplished only with relatively huge doses of hormones.—Author's Summary.

The effect of gonadectomy on the secondary sexual characters of the Bronze turkey (M. gallopavo). Scott, H. M. and L. F. Payne, J. Exper. Zoöl. **69:** 123. 1934.

A marked degree of dimorphism is expressed in the adult plumage of the Bronze turkey. The male possesses the more brilliant feathers of the two sexes. In the young turkey the plumage pattern is non-dimorphic. Bi-lateral removal of the testes exerted no influence on subsequent plumage color or beard growth. Head furnishings were found to be dependent on the male hormone for full expression. Capons were occasionally observed to "strut," although less frequently than the breeding males. Little, if any, difference was observed in spur development 38 weeks following date of castration when compared with the controls. The females following sinistral ovariectomy developed the male type of plumage. This does not agree with the reports found in the literature.—Authors' Abst.

Observations of remissions in hyperthyroidism induced by pregnancy urine extract. Starr, P. and Helen Patton, Ann. Int. Med. **8:** 825. 1935.

Remission of hyperthyroidism occurred in seven young women treated with pregnancy urine extract (antuitrin S and theelin). This remission has now continued for 18 months in the earliest successful case. No recurrence in others has been observed as yet. It is assumed that this effect may be the result of an action of the extract on the ovarian production of theelin. Such treatment failed to bring about remission in 6 other women at or beyond the menopause or in whom interference with ovarian function by surgery or disease has occurred.—R. G. H.

The occurrence of pigment in the pars intermedia and pars tuberalis of the hypophysis, and in the hypophyseal leptomeninges of the rats (domestic and wild). Benjamin, J. A., Anat. Rec. **61:** 331. 1935.

Pigment was found in the pars intermedia and pars tuberalis of the hypophysis in 61 of 532 domestic rats, and 47 of 113 wild rats, and in the hypophyseal leptomeninges in all of the wild and hooded rats studied but in none of the pure albinos. A study of human embryos showed that the connective tissue septa of the pars intermedia and pars tuberalis are formed from the perimedullary mesenchyme, which gives them an origin in common with the meninges. The pigment apparently has its origin in the hypophyseal leptomeninges and migrates to the pars tuberalis and pars intermedia. Evidence is presented which shows that the pigment is inherited. No significance for this phenomenon, particularly with relation to other glands of internal secretion has yet been found.—Author's Abst., Wistar Bib. Service.

A prepubertal reversal of the sex difference in the gonadotropic hormonal content of the pituitary gland of the rat. Clark, Helen M., Anat. Rec. **61:** 175. 1935.

Assays of anterior lobe hormone content were made by implants into immature mice, to determine the extent of variation, with sex and age, of the amount of gonad-stimulating hormone. In the immature rat, from birth to 20 days of age, the gonadotropic hormone content of the anterior pituitary gland was found to be markedly greater in the female than in the male of the same litter. The female maintains this superiority in gland potency, to a less degree, up to the age of puberty, at which period the male gland proves more potent than the female in the majority of cases. From 4 to 6 months of age, the sex difference in pituitary content is negligible, individual determinations showing equal variations in the sex difference, in both directions. By the age of 7 months, the sex difference characteristic of the immature animals, is completely reversed, and the male shows the superiority previously reported by other workers. Separate determinations for each sex, of the changes in single gland content with increasing age, show that (a) in the female, a sharp rise occurs early (13 to 20 days), to a point which is not surpassed, even after full maturity is reached; (b) in the male, a more gradual increase continues up to the age of puberty, to a level which is fairly evenly maintained throughout the period of experiment (10 months).—Author's Abst., Wistar Bib. Service.

A sex difference in the change in potency of the anterior pituitary lobe following bilateral castration in newborn rats. Clark, Helen M., Anat. Rec. **61**: 193. 1935.

The pituitaries of male and female rats, which had been gonadectomized on the first day of life, were assayed 16 to 18 days later for their content of the gonad-stimulating hormone. The assays were made by implantation of a single gland into immature female mice. It was found that the pituitaries from the gonadectomized animals showed a negligible sex difference in gonad-stimulating capacity, in contrast to the normal controls, which showed, as previously reported, a greater potency in the female. The castrated males always showed increased pituitary potency when compared with normal males. The increases averaged 102%. The castrated females showed variable pituitary potencies, fluctuating both above and below the normal females. The average potency of the castrate female pituitary was 19% greater than the normals. The results are considered, together with similar experiments cited on adult animals, as constituting evidence that sex differences in pituitary potency are referable to the differential activity of the gonads, and bear a roughly inverse relation to the amount of hormone being secreted by the ovary and testis.

—Author's Abst., Wistar Bib. Service.

Diabetogenic thyrotropic, adrenotropic and parathyrotropic factors of pituitary. Collip, J. B., J. A. M. A. **104**: 827; 916. 1935. Abst., A. M. A.

The author presents a review of the investigations on the diabetogenic, thyrotropic, adrenotropic and parathyrotropic factors of the pituitary. The diabetogenic effect of the anterior pituitary is due to the combined action of two substances, one acting on the blood sugar level and the other producing ketosis. He shows that the ketogenic substance must be distinct from the thyrotropic principle. A close relationship between the pituitary and the thyroid has been demonstrated clinically. It is concluded that the thyrotropic principle found in anterior pituitary extracts is an entity having physiologic properties that distinguish it from the growth factor, the ketogenic principle, the maturity principle and the adrenotropic hormone. The author has noted that the adrenotropic effect tended to be associated with thyrotropic effect but that with further purification of the thyrotropic principle the adrenotropic action became less. There is as yet no satisfactory physiologic test for the adrenotropic principle; for, since the adrenal cortex reacts with hypertrophy after the administration of numerous nonspecific toxins, the results obtained on normal animals are not conclusive, and the hormone must always be tested on hypophysectomized animals. On theoretical grounds it is conceivable that certain cases of Addison's disease may be due to primary pituitary failure. Two cases of Addison's disease showed marked improvement when adrenotropic extract was administered. It is, of course, not to be expected that cortical tissue that has been damaged by tuberculosis can be activated by pituitary adrenotropic hormone. Clinical evidence for an interrelationship between pituitary and parathyroids has been reported by various investigators. In the author's experience, the parathyroids of hypophysectomized rats and dogs show no consistent degenerative changes, even several months after removal of the pituitary. It is of particular interest in this connection that the simultaneous removal of the hypophysis and the pancreas frequently leads to very marked degenerative changes in the parathyroids of the dog, according to Houssay and Biasotti. Similar observations have been made in the author's laboratory. In some cases large areas of the parathyroids became completely necrotic.

Studies on thyrotropic hormone of anterior pituitary. Collip, J. B. and Evelyn M. Anderson, J. A. M. A. **104**: 965. 1935. Abst., A. M. A.

The authors followed the changes in metabolic rate of a group of rats injected with large doses of a purified extract of thyrotropic hormone. In studying the nature of negative response to the thyrotropic hormone, they have found that the serum of animals which have been injected for a long period of time with thyrotropic hormone contains a substance that is capable of inhibiting the action of thyrotropic hormone. After one month the antithyrotropic substance was found to be present in a horse's serum when it had been injected for a period of four months. Extracts of the antithyrotropic serum of the horse have been prepared which, when given in doses of 0.4 cc., are capable of inhibiting the action of 100 units of thyrotropic hormone in the normal rat. Larger amounts of the extract, up to 4 cc. daily, not only inhibit the action of 100 units of thyrotropic hormone injected into normal rats but at the same

time apparently inhibit the thyrotropic hormone of the animal's own pituitary gland, causing a fall in metabolic rate to minus 24%. The authors have obtained the inhibitory substance in the serum of animals of different species that have been injected with thyrotropic hormone. In addition to the rat and horse, the guinea-pig, rabbit and dog have been studied. The mechanism of the action of the antithyrotropic substance is not understood. It does not inhibit the action of thyroxine. Rats injected with thyrotropic hormone for periods of from 40 to 70 days showed practically the same response to a given amount of thyroxine as normal animals. The giving of antithyrotropic serum in conjunction with thyroxine did not prevent a rise in metabolism. A study of the combined action of the thyrotropic and antithyrotropic hormones on the thyroid may clear up some of the discrepancies between changes in function of the thyroid gland and the cellular activity. When the animal has built up its own antithyrotropic substance as a result of prolonged injections of thyrotropic hormone the thyroid undergoes hyperinvolution until it resembles somewhat the atrophic thyroid seen in the hypophysectomized animal. In an attempt to find the amount of antithyrotropic hormone which would just inhibit the action of a definite amount of thyrotropic hormone, the authors observed that a given amount of antithyrotropic hormone may be sufficient to prevent the rise in metabolic rate without inhibiting the production of hyperplasia of the thyroid by the thyrotropic hormone. Hypophysectomized rats that received both thyrotropic and antithyrotropic hormones for from 7 to 10 days showed hyperplastic changes at the end of this period, associated with a lowered metabolic rate, which was depressed in some instances to 38% below normal. In a large series of rats and guinea-pigs in which they studied the morphologic changes of the thyroid coincident with changes in metabolic rate during treatment with thyrotropic hormone, they found it difficult in many cases to correlate the microscopic appearance with the physiologic changes, as indicated by the metabolic rate. A group of goitrous rats in which the thyroid morphology resembled the hyperplasia seen in exophthalmic goiter showed a subnormal metabolism; in some cases the rates were as low as minus 17%. A severe hyperthyroidism developed in these animals when thyrotropic hormone was given; the metabolic rates varied from plus 120 to plus 200%. The animals that died, death being due apparently to thyrotoxicosis, showed beginning involutional atrophy of the thyroid. Evidence has been gathered in the study of the physiologic properties of the thyrotropic hormone which suggests that the anterior pituitary may play an etiologic rôle in exophthalmic goiter. The finding of an antithyrotropic hormone brings in another factor that needs to be correlated with the present knowledge of thyroid disease. The authors employ in their laboratory methods for assaying the blood serum for the presence of certain inhibitory substances. It appears to them that progress in clinical endocrinology will be more rapid as well as more certain if attention is diverted for the time being from treatment to a study of the blood of the patient so far as reliable methods are available.

The growth hormone of the anterior pituitary. Evans, H. M., J. A. M. A. **104:** 1232. 1935. Abst., A. M. A.

The author believes that an immense step forward was taken by the experimental production of dwarfism when the gland was removed from young animals. The classic experiments of Aschner, which were done with puppies with littermate controls, showed that an immediate arrest of growth and development was occasioned by the operation. It was conceivable, of course, that the dwarfism following hypophysectomy was a secondary effect; i.e., that it was due to some obscure metabolic upset consequent on loss of the gland rather than the direct outcome of the elimination of a specifically needed substance that could be justifiably called the growth hormone. It was perhaps fortunate, then, that experimental evidence of the existence of the growth hormone had been secured by the production of gigantism in normal animals. The gigantism or accelerated growth that may thus be induced by anterior pituitary extracts in the rat is an extreme one. Obscure but indubitable is the continued need on the part of the body for the growth hormone in adult life. The glands of grown cattle yield proportionately the same amount of growth hormone as do those of rapidly growing young calves. The endocrinologist is already acquainted with the continuous production of blood cells throughout adult life and the replacement of cells lost through attrition at the intestine and skin surfaces, but these processes are apparently not significantly impaired in hypophysectomized animals. The distortion of growth in adult life that produces the disease called acromegaly is well known. The classic explanation of the disorder has been that growth has been imposed on the skull and extremities

when stature changes are impossible because of epiphyseal closure. Should one learn to close prematurely the epiphyseal disks of rats, one might hope to make them acromegalic; but there are some serious objections to this simple explanation of the situation. One of the greatest needs in growth hormone research is the discovery of a specific biologic test for the hormone that can be rapidly performed. At the present time two reliable tests are known and are employed in the detection of the growth hormone. They are done by the use of adult normal female rats or hypophysectomized rats of either sex. Even though growth deficiency often seems the sole outstanding defect, in all cases of dwarfism the output of other hypophyseal hormones may be subnormal, and it is probable that future research will establish the fact that medication with more than a single hormone is indicated. Recent biologic experimentation itself has begun to speak decisively for the improvement of growth when in addition to the growth hormone other hormones are concurrently administered. There is no information yet as to whether the growth hormone acts directly on the widespread tissues of the body which it stimulates to increase. The improved appetite of normal animals under the influence of the growth hormone is always strikingly evidenced by the increased food consumption, but the unusual growth produced by the growth hormone is not referable to so simple an explanation. The exact mechanism of action of the growth hormone on metabolism remains entirely unknown, but a significant beginning has been made in the analysis of its effects. The study of Lee and Schaffer showed that treated animals do not possess the characteristic age changes that normal rats exhibit (decreases in the proportion of water, nitrogen, fat-free dry tissue and ash, and increases in the percentage of fat) but retained with considerable exactitude their initial composition in certain chemical constituents. This propulsion of growth in the rat's adult life is therefore associated with the retention of certain juvenile chemical characteristics in the tissue produced, and the question naturally arises as to whether the "youthfulness" of this tissue indicates "youthfulness" of the animal with regard to expectance of a correspondingly longer life span. Other studies, such as those of the physiologic performance of such animals have not yet been made. Possible changes in the mental acuity of animals forced to continue maximal growth have not as yet been investigated. The growth hormone is probably itself a protein or so closely associated with protein as to make its separation from protein extremely difficult. The purest forms of it heretofore available when analyzed continue to contain about 16% of nitrogen and to give most of the classic qualitative tests for protein. For extracting the hormone from anterior lobe tissue, all workers continue to employ dilute aqueous alkali, the method originally introduced by Evans and Simpson. The problem of preliminary purification resolves itself into separation of the hormone from the greater part of the contaminating protein with which it is associated.

Vitamin C in the hypophysis (La vitamine C dans l'hypophyse). Giroud, A. and C. P. Leblond, Compt. rend. Soc. de biol. **116**: 629. 1934.

Employing the silver nitrate technic, the authors were able to demonstrate conclusively the presence of large quantities of vitamin C in the chromophilic cells of the anterior lobe of the hypophysis. Less ascorbic acid was found in the intermediate lobe, and least in the nervous lobe. The determinations were made on several species of animals; only the ox is mentioned specifically.
—J. C. D.

Isolation of the thyroid-stimulating substance of anterior pituitary extracts by digestion of the crinogenic substance by pepsin (Isolement de la substance thyréostimulante des extraits préhypophysaires par digestion pepsique de la substance crinogène). Guyénot, E., K. Ponse and E. Dottrens, Compt. rend. Soc. de biol. **116**: 92. 1934.

The crinogenic (luteinizing) and thyroid-stimulating properties of the anterior lobe of the hypophysis belong to two different substances. In an acid medium pepsin will destroy completely the luteinizing substance. A third substance with auxogenic properties can be separated from the other two by filtration.—J. C. D.

Action of pitressin upon circulation and respiration. Hartl, K., Arch. f. exper. Path. u. Pharmakol. **173**: 133. 1933.

Pitressin was injected into men and its effect on the circulatory and respiratory systems studied. There was an increase found in the systolic and

diastolic blood pressure, peripheral resistance and amplitude of the pulse with an augmentation in the ventilation of the lungs. There was a lessened membrane permeability and an increase in the oxygen debt found during work. —L. B. Nice.

Rôle of the hypophysis in the hyperglycemic action of the blood of the diabetic dog (Rôle de l'hypophyse dans l'action hyperglycémiante du sang de chien diabétique). Képinov, L., Compt. rend. Soc. de biol. **116:** 145. 1934.

A carotid-jugular anastomosis was effected between a normal and a hypophysectomized and pancreatectomized dog. The blood of the normal dog showed no tendency toward hyperglycemia. Injection of anterior pituitary extracts into the hypophysectomized dog of the pair did produce hyperglycemia in the normal dog. It was concluded that normally the functions of the pancreas are antagonistic to those of the hypophysis in the normal regulation of glycemia.—J. C. D.

Procedure for the destruction of the hypophysis of the rabbit by radium (Procédé de destruction de l'hypophyse du lapin par le radon). Lacassagne, A. and W. Nyka, Compt. rend. Soc. de biol. **116:** 581. 1934.

The frontal bone is trephined in the mid-line. A needle introduced through the orifice penetrated the meninges and was passed between the frontal lobes to the sella turcica. The radium in the needle is then discharged. This technic has been used successfully by the authors.—J. C. D.

Experimental change of the gonadotropic equilibrium of the anterior hypophysis (Changement expérimental de l'équilibre préhypophysaire gonadotrope). Lipschütz, A., Compt. rend. Soc. de biol. **116:** 89. 1934.

Fourteen to 16 mg. of anterior pituitary of adult male rats previously injected with folliculin were administered to 7 immature female rats. Four immature female rats from the same litters received the same amounts of anterior pituitary from normal adult males. All of the rats of the first group underwent estrus characterized by epithelial and keratinized cells; animals of the second group showed only leucocytes. Ovaries of the first group were of the characteristically immature type; without exception those of the second group presented luteinization. Thus injection of folliculin into normal adult male rats decreased the luteinizing power of the anterior pituitary, but augmented the estrogenic power.—J. C. D.

Five types of hypopituitary endocrinopathies. Loewenberg, S. A., M. Clin. North America, **17:** 647. 1933.

This is an excellent summary of the physiology of the pituitary, with 5 case histories each representing a clinical type of pituitary disorder. Case 1 is that of infantilism without adiposity (Lorain-Levy type) occurring in a female of 28. Her height was 52 inches and weight 48 pounds. The second case is one of hypopituitarism with cryptorchism occurring in a male of 34. His height was 56 inches. Case 3 is that of dystrophia adiposa genitalis occurring in a single woman of 26 whose height was 5 feet 6 inches and weight 300 pounds. Case 4 is that of cerebral obesity occurring in a married woman of 32, weighing 400 pounds, and whose height is 4 feet 9 inches. Case 5 is that of adiposis dolorosa (Dercum's disease) with epilepsy in a woman weighing 380 pounds.—I. B.

Minerals of plasma in hypophysectomized dogs (Sustancias minerales del plasma de los perros hipofisoprivos). Marenzi, A. D. and R. Gerschman, Rev. Soc. argent. de biol. **10:** 131. 1934.

Determinations were made in 6 hypophysectomized dogs, 1 to 10 months after operation, and in 9 to 22 normal controls. No significant variations were found in the plasma content of CO_2, Cl, P, Na and Ca and in cell volume; K was diminished (—18.5%) also Mg. (—11.5%).—J. T. L.

Lactic acid in blood of hypophysectomized dogs (Acido láctico sanguíneo de los perros hipofisoprivos). Marenzi, A. D., Rev. Soc. argent. de biol. **10:** 121. 1934.

Lactic acid in blood taken after a 12-hour fast was determined by Friedman, Cotonio and Shaffer's method. Hypophysectomized dogs, 1 to 7 months after operation, gave a mean value of 17.8 mg. per cent (14 experiments); the average in 18 normal controls was 18.3 mg. per cent.—J. T. L.

Method for staining the anterior lobe of the hypophysis (Sur les méthodes de coloration histologique de l'hypophyse antérieure). Martins, T., Compt. rend. Soc. de biol. **113:** 1275. 1933.

The method described was devised for glands of small animals. The glands are fixed in Helly's fluid, then treated with iodine, stained with hematoxylin, followed by acid fuchsin and phosphomolybdic acid and, finally, methylene blue. This differentiates the three types of cells.—J. C. D.

Effect of oestrin and gonadotropic hormone injections upon hypophysis of the adult rat. Nelson, W. O., Proc. Soc. Exper. Biol. & Med. **32:** 452. 1934.

The pituitaries of 130 male and 114 female rats injected with oestrin, Antuitrin-S, pituitary extract, or pregnant mare serum were studied after either histological or cytological preparation. In non-castrate animals of both sexes all of the above treatments induce a marked decrease in the granulated basophiles and an increase in degranulated and chromophobic cells. Degranulation is also observed in the acidophiles. In castrate animals only oestrin induces these changes, indicating that the gonadotropic preparations exert their effect through their action upon the gonads.—Author's Abst.

Anterior pituitary and anterior pituitary-like substances; therapeutic applications. Novak, E., J. A. M. A. **104:** 998. 1935. Abst., A. M. A.

The author states that the employment of the growth hormone preparations is indicated in the various types of pituitary growth deficiency. The results are usually not striking and will probably not be improved until biochemists isolate the hormone and produce more potent preparations. The anterior pituitary-like preparations are probably of no value when used alone in the treatment of amenorrhea, and even when combined with estrogenic substance the results are very little improved. The anterior pituitary-like preparations made from pregnancy urine have appeared to give excellent results in many, though not by any means all, cases of functional uterine bleeding, so that when this disorder is encountered in young women, in whom radiotherapy is undesirable, the method should certainly be tried. The comparatively small group of cases thus far reported in which the undescended testicle has been successfully treated by the anterior pituitary-like preparations make this method seem promising and worthy of a more extended trial, especially as the surgical treatment of this conditioin is not as satisfactory as might be wished. There is no objection to a trial of the anterior pituitary-like preparations in the occasional mysterious and baffling cases of habitual abortion, although the results are not much more clearly defined than is the etiology of the condition. These preparations appear rational as adjuvants in the treatment of primary dysmenorrhea, although correction of constitutional and psychic factors is often much more important, and should never be overlooked. As to other conditions, such as aspermia and baldness, the clinical data thus far available are much too meager to draw conclusions as to the results of treatment with the anterior pituitary-like preparations, and there are physiologic reasons to make one question the value of this plan. It is possible that the results of organotherapy in various forms of anterior hypopituitarism may be improved with preparations of the gonad-stimulating hormones obtained from the anterior lobe itself.

The effects of the pituitary hormones on the melanophores of fishes. Odiorne, J. M., Proc. Nat. Acad. Sc. **19:** 745. 1933.

Spaeth (1918) reported that the melanophores on isolated scales of Fundulus heteroclitus contract when the scales are placed in solutions containing "pituitrin," and Wyman (1924) observed that these fishes became light following injections of "pituitrin," yet similar experiments described in the present paper have given negative results. The melanophores of isolated scales contract in distilled water and expand in Ringer's solution; the addition of

"pituitrin" has no effect in either case. When "pituitrin" (0.1 to 0.4 cc.) is injected into the body cavity of specimens of Fundulus they continue to respond to backgrounds like normal uninjected fishes. Though "pituitrin" has no effect on the melanophores of Fundulus, those of catfishes (Ameiurus nebulosus) expand following the intraperitoneal injection of "pituitrin" and "pitressin"; "pitocin" has no effect. The melanophores of eels and black-backed goldfishes also expand following intraperitoneal injections of "pituitrin" and "pitressin." When "antuitrin" is injected into specimens of Fundulus, and when isolated scales are placed in Ringer's solution containing this extract, the melanophores do contract. This suggests that the results obtained by Spaeth and by Wyman, who used extracts supplied to him by Spaeth, were due to the presence of substances from the anterior lobe in the post-pituitary preparations. Whatever the explanation of the discrepancy may be, it is evident from these experiments and from experiments performed by other investigators on different fishes, that not all fishes respond in the same way to pituitary preparations. Possibly the differences in the responses are somehow related to the varying importance of the nervous system and the humoral system in these forms. At the same time it seems clear that the responses of the melanophores of fishes and amphibians are not fundamentally different, though Spaeth's observations led Hogben (1924) to this conclusion.—Author's Abst.

The weight of the principal components of the normal hypophysis cerebri of the adult human female. Rasmussen, A. T., Anat. Rec. **55:** 253. 1934.

Volumetric data by the paper-weight method on hypophyses of 93 non-pregnant women 16 to 84 years of age, from cases of sudden accidental death, gave the following weights in milligrams. Anterior lobe—range, 335 to 836; mean, 499 ± 6.2; standard deviation, 88.7; coefficient of variation, 18. Posterior or nervous lobe—range, 67 to 176; mean, 110 ± 1.6; standard deviation, 22.9; coefficient of variation, 21. Epithelium (parenchyma) of pars intermedia —range, 0.3 to 19.5; mean, 3.4 ± 0.2; standard deviation, 2.9; coefficient of variation, 85. Colloid—range, from almost nothing to 62; mean, 6.1 ± 0.7; standard deviation, 10.5; coefficient of variation, 172. Whole gland (without capsule, infundibulum and pars tuberalis)—range, 448 to 971; mean, 618 ± 6.6; standard deviation, 94.2; coefficient of variation, 15. In women the hypophysis tends to retain its weight in old age better than in men. Women have a larger anterior lobe than men. There is a positive correlation between stature and weight of the anterior lobe. Anterior lobe enlarges during pregnancy (24 cases). The anterior lobe represents 80% of hypophysis in non-pregnant and 84% in pregnant women. The nervous lobe constitutes 18% in non-pregnant and 15% in pregnant women. Pars intermedia (including colloid) is only 1½% of the organ in non-pregnant and 1% in pregnant women. Morphologically there are no indications of hyperactivity in pars intermedia during pregnancy.—Author's Abst., Wistar Bib. Service.

Responses of the reproductive system of hypophysectomized and normal rats to injections of pregnancy-urine extracts; the male. Smith, P. E. and S. L. Leonard, Anat. Rec. **58:** 145. 1934.

Extracts of pregnancy urine were injected for 5-60 days into hypophysectomized and normal mature and immature male rats. Treatment of the hypophysectomized rats was begun both at the time of operation and after a lapse of 20-75 days. The injections in the operated males either maintained testicular weights or profoundly slowed the atrophy which characteristically takes place after pituitary ablation. They induced an hypertrophy of the interstitial tissue and accessory organs both in the normal and the operated males. In the operated animals the hypertrophy decreased by the 30th day of treatment. In mature hypophysectomized rats, injections begun at the time of operation maintained spermatogenesis and, in most cases, mating and fertility. In immature rats, 31-34 days old at operation, the injections continued the development of the tubules. In mature and immature rats, injections begun 20-75 days after hypophysectomy induced an increase in the weight of the testes, enlargement of the tubules and an increase in the activity of the germinal epithelium. In only one of the four animals were spermatids formed. The injections did not hasten maturity in normal males. The tubules were not injured in either the mature or immature normal males. In the mature males intratubular columns of typical spermatogenic cells were infrequently found. —Authors' Abst.

The normal level of the various cell types in the anterior pituitaries of mature and immature rats and further observations on cyclic histologic variations. Wolfe, J. M., Anat. Rec. **61**: 321. 1935.

The anterior pituitaries of 143 normal female rats sacrificed during the different phases of the oestral cycle were studied and differential cell counts made. There were definite cyclic morphologic changes in the basophilic cells. Basophiles containing granules were abundant during prooestrus and in the transition from prooestrus into oestrus. In full oestrus, however, practically all basophiles exhibited marked granular loss. In metoestrus practically all the basophiles were non-granular, but in dioestrus there was a partial restoration of the granular basophiles. There were no definite morphologic changes in the eosinophiles during the normal oestral cycle of the rat. In 115 of the 143 rats studied the level of the eosinophiles was between 30 and 40%, while in 129 the level of the basophiles was between 2 and 5.9%. The anterior pituitaries of 15 immature female rats killed at 17 days of age and of 53 rats killed between 27 and 35 days of age were studied. The level of the eosinophiles in the immature animals was practically the same as that found in the mature females. Basophiles were much more abundant in the anterior pituitaries of the immature animals, however. They exhibited little granular loss. Mitoses were found in all groups of rats. The pituitaries of mature rats killed in oestrus were slightly heavier relative to body weight.

—Author's Abst., Wistar Bib. Service.

Morphological studies of the anterior pituitaries of mature female rats receiving injections of pregnancy urine extracts. Wolfe, J. M., E. T. Ellison and L. Rosenfeld, Anat. Rec. **60**: 357. 1934.

Forty-four female rats received injections of from 25 to 75 units of an extract of pregnancy urine daily for 15 days. The ovaries and the pituitaries were markedly increased in weight. Histologically, the anterior pituitaries showed extreme granular depletion of the basophiles and moderate to extreme granular depletion of the eosinophiles. Cell counts revealed that the relative percentage of the basophiles and the eosinophiles was decreased, while that of the chromophobes was increased. Colloid was found in the residual cleft of practically all glands. Mitotic activity was marked.

—Authors' Abst., Wistar Bib. Service.

Endocrine reactions in dogs with experimentally produced pancreatic diabetes (Réactions endocriniennes chez les chiens atteints de diabète pancréatique expérimental). Binet, L., J. Verne and R. Messimy, Compt. rend. Soc. de biol. **116**: 812. 1934.

Certain constant histological manifestations of some endocrine glands supposedly consequent to pancreatectomy in dogs (number not stated) are discussed. The anterior lobe of the pituitary contains a predominance of eosinophilic cells with numerous mitochondria; the intermediate lobe possesses many cysts filled with colloid; the nervous lobe reveals an excessive quantity of colloid. In the thyroid the vesicles are characteristic of hyperactive glands. The medulla of the suprarenal is normal, but the cortex shows a pronounced discharge of lipoids in all three of its zones.—J. C. D.

The humoral nature of insulin resistance (Uber die humoral Natur der Insulinresistenz). Boller, R., K. Uiberrak and W. Falta, Wien. Arch. f. inn. Med. **25**: 25. 1934.

After a subcutaneous injection of insulin into normal individuals, the insulin can be demonstrated in the blood stream by the use of the transfusion method into diabetics sensitive to insulin.—H. J. J.

Differential inactivation of insulin. Davis, B., Jr., J. M. Luck and A. G. Miller, Biochem. J., **27**: 1643. 1933. Abst., Chem. Absts **28**: 1725.

Inactivation of insulin by acid-alcohol and by soft x-rays shows that the phosphate-lowering activity of insulin is the most resistant to destruction. Massive doses of insulin inactivated by x-rays produced hyperglycemia. Insulin owes its multiple activity to a number of "active groups," which vary in stability toward inactivating agents.

Treatment of diabetes with insulin (after ten years); contrasting effects of normal and of older diabetic diets. Geyelin, H. R., J. A. M. A. **104:** 1203. 1935. Abst., A. M. A.

The author summarizes the results of treatment in a group of 150 cases of diabetes treated with insulin and a high carbohydrate diet during the past ten years. Patients treated with high carbohydrate-low fat diets achieve greater effectiveness of insulin as judged by the ratio of units of insulin to grams of carbohydrate oxidized. The administration of such diets overcomes hypercholesterinemia. In the majority of instances, blood sugar levels are reduced after the administration of high carbohydrate diets. Hyperinsulinism is less common and less severe. Complicating conditions such as tuberculosis, gangrene and cardiovascular disease are less common when patients are being treated with the high carbohydrate diet (normal calories). After ten years of application of the high corbohydrate diet, the majority of patients show no loss of food tolerance or any other demonstrable retrogression of the diabetes.

Insulin—its use in non-diabetic children. Higgins, R. A. and E. O. Ostlund, J. Pediat. **5:** 494. 1934.

Insulin therapy is of real value in speeding up the rate of gain of undernourished children who do not respond satisfactorily to the usual hygienic and dietary treatment but it has very little effect on the weight curve of children who are already gaining at a satisfactory rate. Any weight gain may be maintained for at least two months. The usual dose is five units t.i.d. but it may be necessary to increase this in certain cases. The administration of 20 units before meals is relatively safe in children over three years of age. Very young children and infants do not react favorably to continued therapy because of the frequency with which they are thrown into hyperglycemic shock.—M. B. G.

Temporary visual disturbances as an initial symptom of diabetes mellitus. Himsworth, H. P., Brit. M. J. **2:** 1184. 1932. Abst., Arch. Neurol. & Psychiat. **31:** 1111.

This study is based on 100 cases of diabetes mellitus, in which each patient was examined specifically for disturbances of vision. In each case the eyes were examined by the retinoscope and the ophthalmoscope. All patients showing gross organic damage such as cataract, retinitis and hemorrhages into the vitreous were excluded. The cases were divided into two groups, those occurring in persons under 45 and those in patients over that age. In the first age group a history of temporary visual disturbance was given in 49% of the cases, and in the second group, in 21% of the cases. Thus, temporary visual disturbances, apparently referable to changes in refraction, have occurred as an initial symptom in 34% of these 100 cases of diabetes. All cases had this in common: the derangement of vision was only temporary. The symptom has never been reported in cases of glycosuria which on investigation have been found not to be cases of diabetes. In eight proved cases of renal glycosuria it was absent. Thus, it seems permissible to conclude that rapid changes of refraction are in themselves sufficient for a diagnosis of diabetes mellitus, though this deduction could not be securely accepted unless it was fully proved by many observers that similar visual disturbances are never found in other diseases.

Viability of totally pancreatectomized dogs treated with duodenal extracts (Maintien en vie de chiens totalement dépancréatés traités par les extraits duodénaux). LaBarre, J. and J. Ledrut, Compt. rend. Soc. de biol. **115:** 1233. 1934.

The product of hydrolysis of secretin was administered orally to 4 pancreatectomized dogs. Their daily diet contained in addition to this product a quantity of glucides, proteids, and lipides. By this regime the the animals were kept in good health for more than 2 months.—J. C. D.

Diabetes and cancer. Marble, A., New England J. Med. **211:** 339. 1934.

Analysis is made of 256 cases in which malignant disease and diabetes were associated. These represent cases recognized among 10,000 diabetic patients. Among the fatal cases, the average duration of diabetes was 7.1 years. The average duration of symptoms of cancer was 1.8 years. The conclusion is drawn that in general, cancer develops in the diabetic and not diabetes in the patient with cancer. Evidence is lacking that cancer brings about the diabetic

condition. Study of available data shows that the increasing percentage of cancer deaths to total deaths during the last two decades is greater among diabetics than among members of the general population. This is thought to be due, in part, at least, to the fact that the increased longevity of diabetic patients during the last decade has placed relatively more diabetics than non-diabetics in the cancer age-zone. It does not necessarily imply that the diabetic is any more likely to develop cancer than the non-diabetic individual. The series includes 33 cases of carcinoma of the pancreas of which 21 were diagnosed either at operation or autopsy. The evidence of carcinoma of the pancreas was therefore extraordinarily high. In this series it was 12.9% of the total number of cases as contrasted with less (often considerably less) than 5% in general cancer statistics reported by others. The average duration of symptoms of cancer in the 21 proved cases of carcinoma of the pancreas was 1.0 years; in these same cases the average duration of diabetes was 3.4 years. This latter figure represents the shortest duration of diabetes of any group of diabetics under observation. Thus a possible relationship between cancer of the pancreas and diabetes is suggested. Figures from the literature (general hospital series), however, tend to indicate that diabetes is relatively uncommon in cases of carcinoma of the pancreas.—Author's Summary.

Psychological factors in the etiology of diabetes. Menninger, W. C., J. Nerv. & Ment. Dis. **8:** 1. 1935.

Menninger comments upon the possibility of emotional glycosuria being exaggerated to the point of actual diabetes. He reports upon 22 cases in which mental disorder and diabetes were noted simultaneously. In most of the cases coincidence was not excluded as explaining the relationship but in five cases there was a close parallelism between the degree of disturbance of the carbohydrate metabolism and of mental disturbance. With the cure of the latter the diabetes cleared up. It is suggested that in cases having other than emotional etiology the course of established diabetes may be significantly modified by psychologic factors.—R. G. H.

Effect of oestrin injections upon experimental pancreatic diabetes in the monkey. Nelson, W. O. and M. D. Overholser, Proc. Soc. Exper. Biol. & Med. **32:** 150. 1934.

In two female monkeys hyperglycemia and glycosuria were induced by the injection of an anterior-pituitary extract. In four animals the pancreas was removed. In two cases oestrin injections had been given for two weeks prior to pancreatectomy, while in the other two oestrin was given only after the diabetic condition was established. In all cases a marked decline in glycosuria and hyperglycemia was noted during the periods of oestrin injection.
—W. O. Nelson.

Insulogenic stimulation of sexual development. Williams, G. A. and R. L. Williams, J. A. M. A. **104:** 1208. 1935. Abst., A. M. A.

The authors point out that the administration of insulin to a poorly developed nondiabetic girl 8½ years of age resulted in striking acceleration of body growth and sexual development. This was manifested by increase in height and weight, stimulation of the mammary glands, ovaries and uterus, assumption of the adult type of fat distribution, and a growth of fine body hair. Discontinuance of insulin was followed by prompt regression of secondary sexual phenomena. Body growth continued, but at a less rapid rate. Resumption of insulin after a lapse of ten months resulted in prompt reappearance of the sexual phenomena, to regress as soon as insulin was again omitted.

Roentgenographic studies of parathyroid deossification. Moore, J. J. and A. A. de Lorimier, Am. J. Roentgenol. **31:** 496. 1934. Abst., Surg., Gynec. & Obst. **59:** 333.

The authors present a brief review of the literature on the skeletal changes accompanying hyperplasia of the parathyroid glands and parathyroid tumors and describe in detail the roentgenographic changes occurring in the bones of rabbits given doses of parathyroid extract. In addition to x-ray studies, observations were made on the calcium and phosphorus balance in the experimental animals. Three groups of rabbits were studied. Those of Group 1

were used as controls. Those of Group 2 were given varying doses of ammonium chloride, which produced a more or less severe acidosis, and those of Group 3 were given sodium bicarbonate in an amount sufficient to cause a marked alkalosis. The removal of bone salts following the administration of parathyroid extract was most marked in the animals in which acidosis had been produced and least marked in the animals given sodium bicarbonate. On the basis of the x-ray pictures, the authors distinguish three stages in the deossification changes following the administration of parathyroid: (1) A substitution of trabeculation shelves for either the amorphous deposits or for the intersecting trabeculations of the medullary metaphyseal region. (2) A thinning of the cortices, manifested both by an increase in the radiolucency and a coarsening of the cortical trabeculations, especially in the metaphyseal regions. (3) An even greater resorption, a further thinning of the cortices, manifested by: (a) very marked radiolucency, (b) depletion of the "trabeculation framework" and perhaps local evidences of cystic dissolution, and (c) thinning of the epiphyseal cancellations.

Calcium and phosphorus studies; effect of diet and viosterol on tetany and on serum calcium of parathyroidectomized rats. Shelling, D. H. and Dorothy E. Asher, J. Biol. Chem. **96:** 215. 1932.

Viosterol was given in large doses (from 20 up to 80,000 times the therapeutic dosage) to parathyroidectomized rats. Even when the diet was low in calcium, this resulted in rises of the blood calcium, sometimes to hypercalcemic levels; severe tetany was relieved, the weight-curve showed an upward turn, and calcification of soft tissues (e.g., heart) could be produced. Therefore viosterol acts independently of the parathyroids.—F. T. Jung.

Pinealectomy in rats, with a critical survey of the literature. Anderson, Dorothy H. and O. Wolf, J. Physiol. **81:** 49. 1934.

The literature covering the effects of pinealectomy upon growth and reproduction in the rat, guinea-pig, rabbit, dog, fowl, and frog is reviewed. Attention is called to the absence of agreement and the lack of statistical analyses in the earlier studies. In the present study 125 carefully standardized rats were divided into three groups which included 58 operated, 37 operated controls, and 30 normal controls. All operations were performed when the animals were 1 to 3 days old. In both operated and operated control groups the mortality was about 50%. The animals were sacrificed between the ages of 60 and 90 days. Observations, including growth, vaginal opening, oestrous cycles, sperm maturity, and the weights of the various endocrine glands, were made. Statistical treatment of the results showed no significant difference between the three groups. It is concluded that pinealectomy exerts no influence upon growth, puberty, or the weight of pituitary, thyroid, adrenal, thymus, and testis.—W. O. Nelson.

Acceleration of growth of newborn rats obtained by oral administration of deproteinized placental extract to the mothers (Accélération de la croissance obtenue chez les rats nouveaunés par l'administration à leur mère d'un extrait placentaire buvable déprotéiné). Arthus, A., Compt. rend. Soc. de biol. **115:** 1092. 1934.

The weight of newborn rats of mothers (numbers not stated) whose normal diet contained deproteinized placental extract was found to increase steadily over that of newborn rats whose mothers' diet did not contain the extract. The litters were weighed daily for 11 days.—J. C. D.

Epithelial alterations and lymphocytic infiltrations in the human thyroid (Altérations épithéliales et infiltrations lymphocytaires dans la thyroïde humaine). Bastenie, P., Compt. rend. Soc. de biol. **116:** 656. 1934.

Seventy-five thyroids from patients with colloid goiter, exophthalmic goiter, etc., were studied histologically. Lymphocytic infiltrations were never present in normal zones, but only in regions of chronic inflammation characterized by disintegration and ultimate sclerosis of glandular elements.

—J. C. D.

Total ablation of thyroid in angina pectoris and congestive failure; summary of results in treating seventy-five patients during the last eighteen months. Blumgart, H. L., D. D. Berlin, D. Davis, J. E. F. Riseman and A. A. Weinstein, J. A. M. A. **104:** 17. 1935. A. M. A.

The authors summarize their experience during the last eighteen months in treating 75 patients with chronic heart disease by removing the entire normal thyroid. Their summary embodies (1) clinical appraisal of the therapeutic value of the procedure, (2) establishment of criteria for the proper selection of patients, (3) reduction in the risk of operation through study of the surgical technic and the best possible preoperative and postoperative care, (4) study of the mechanisms whereby the development of hypothyroidism results in relief of angina pectoris and congestive failure and (5) investigation and control of the secondary consequences of the hypothyroid state. Although final conclusions concerning these problems await the results obtained over a period of years, the authors believe that it may be helpful to state the results based on their present experience. Of the 75 patients, 50 wre treated primarily for recurrent congestive failure of rheumatic, arteriosclerotic, hypertensive, congenital or syphilitic etiology. The ages of the patients ranged from 18 to 69 years. Twenty-four of these patients have maintained compensation and have shown decided improvement for from two to eighteen months. For the first time in from months to years they are up and about the entire day without discomfort and without reappearance of the signs or symptoms of congestive failure. Four patients are able to undertake only light work, while 20 patients are living a life of moderate activity, and, although not indulging in heavy labor, many are economically rehabilitated. In more than half of these patients the postoperative period ranges from six to eighteen months; 8 have maintained their compensated state for more than a year. Of the 24 patients with congestive failure who have maintained their improvement, 4 are able to undertake only light work. The average duration of postoperative improvement in these 4 patients is seven and one-half months. Two patients have shown little or no improvement following operation. Congestive failure recurred temporarily in 6 patients after operation. Of the 75 patients with chronic heart disease, angina pectoris was present in 32. In 19 of these, the anginal syndrome was the major disabling factor. In the remaining 13 patients, angina pectoris was overshadowed in 5 patients by cardiac asthma, and in 8 by congestive failure. Of the 32 patients who suffered from angina pectoris, the condition was sufficiently pronounced in 25 so that the therapeutic effects of the operation on this syndrome could be evaluated definitely. The etiology of angina pectoris was arteriosclerotic or hypertensive in 23 patients and rheumatic in 2. The ages of the patients ranged from 41 to 70 years. Of the 25 patients, 8 patients have had no recurrence of attacks of angina in spite of activity for from three to eighteen months after operation and have required no glyceryl trinitrate. The average duration of complete relief in these patients is ten months. Of the remaining 17 patients, 5 have experienced only occasional attacks since operation, are capable of undertaking considerably more activity than was previously possible and have returned to remunerative occupations or housework. The average duration of moderate relief in these 5 patients is ten months. Two patients, completely relieved of anginal attacks for four and nine months, recently have suffered recurrence of attacks following an automobile accident in one instance and coronary occlusion in another. Three other patients, after striking improvement, recently have had recurrences of attacks coincident with excessive rise in metabolic rate induced by thyroid. This medication has now been discontinued. One patient, a woman, aged 70, confined to bed before operation because of angina pectoris and cardiac asthma, was completely free of symptoms for three months after operation, when she suffered coronary occlusion and died. There have been no other subsequent deaths in patients with angina pectoris. Four patients have shown no increase in their exercise tolerance and still have attacks of angina, which are as frequent but less severe than before operation. These patients have not been able to return to work, and the results do not justify the operative procedure. In this group of four, three patients showed preoperative metabolic rates of minus 19, minus 23 and minus 24% and, in view of considerations elsewhere discussed, would not now be operated on.

A method for the investigation of the impedance of the human body to an alternating current. Brazier, M. A. B., J. Inst. Elec. Eng. **73:** 204. 1933. Abst., Physiol. Absts **18:** 588.

A technique is described for carrying out measurements of the impedance angle of the human body. It is shown that this is a measurement of true

physiological significance, independent of electrode and skin effects. A study is made of the impedance angle in the normal subject, and reference is made to an investigation in which it has been shown that in cases of thyrotoxicosis there is a correlation between the impedance angle and the basal metabolic rate. The variation of impedance angle in thyrotoxicosis is a reliable aid to the diagnosis of this disease.

Iodine content of blood and of urine and basal metabolic rate; their value in the diagosis of the function of thyroid gland. Elmer, A. W. and M. Scheps, Acta. med. Scandinav. **82:** 126. 1934.

The blood iodine and urinary iodine excretion were determined in the following 5 groups of patients: (1) Nine patients, non-thyroid, with normal basal metabolic rate. The blood iodine varied from 8-19γ per cent and the iodine excretion approximated 30γ in 24 hours. (2) Ten patients with metabolism fluctuating from minus 18 to minus 38%, not due to thyroid disease. The blood iodine level ranged from 9 to 18γ per cent and the excretion in 24 hours from 18 to 44γ. (3) Eleven patients with non-toxic goiter, associated with normal or decreased metabolism. The blood iodine and urinary iodine excretion were within normal limits. (4) Eight patients with hyperthyroidism. The blood iodine content varied from 20 to 112γ per cent, but did not parallel the metabolic rate. In individual patients, clinical and metabolic improvement under therapy was associated with a decrease in blood ioidine. The excretion of iodine was increased, varying from 21 to 136γ. (5) Seven patients with hypothyroidism. The typical cases of myxedema had a decreased blood iodine (4-6γ per cent); the atypical forms had iodine values at the lower limits of normal. The iodine excretion in myxedema was normal. It is concluded that the determination of the blood iodine is of value in the diagnosis of hyperthyroidism only in conjunction with the basal metabolic rate. A low blood iodine, in the absence of therapy, excludes hyperthyroidism. The determination of blood iodine is of limited value in the diagnosis of hypothyroidism.

—J. Lerman.

Roentgen therapy versus surgery in the treatment of hyperthyroidism. Farrell, J. T., Jr., Pennsylvania M. J. **38:** 484. 1935.

Farrell compares roentgen-ray with surgical methods of treatment of hyperthyroidism based on observations upon 94 cases treated by roentgen therapy. He believes that roentgen therapy is accompanied by less inconvenience to the patient than is surgery. There is no pain, little fear, and no postoperative sequelae if patients are treated by roentgen rays. Often patients do not give up their usual activities while undergoing roentgen-ray treatment. With surgical treatment there is always a period of confinement to bed. When rest is practiced as a supplement to roentgen therapy it may be carried out at the home of the patient without the expense and inconvenience of hospitalization. Roentgen therapy is practically devoid of danger whereas complications of thyroidectomy and other surgical procedures are numerous and of serious import. Myxedema is more common as a result of surgery than of roentgen therapy; it is an extremely rare sequel of roentgen therapy. Although in the hands of experienced operators the mortality rate of thyroid surgery is low, it is always present. In the less experienced it rises to formidable proportions. The mortality rate following roentgen therapy is practically nil. The end results of roentgen therapy compare favorably with those of surgery. In those cases in which roentgen therapy fails to bring about a cure surgery is not made more difficult. In those cases in which surgical procedures fail to bring about improvement, roentgen therapy may lead to cure. Probably all patients suffering from hyperthyroidism should be given roentgen therapy before being subjected to the inconveniences and dangers of thyroid surgery.—I. B.

The influence of the thyroid on the action of gonad-stimulating hormones. Fluhmann, C. F., Am. J. Physiol. **108:** 498. 1934.

The administration of acid gonad-stimulating extracts made from sheep, rat or human anterior hypophyses resulted in an increase of the rate of oxygen consumption of immature white rats. With larger doses the sheep anterior lobe extract produced a hyperplasia of the thyroid gland. The injection of an acid gonad-stimulating extract made from blood of pregnant women resulted in a diminution of the rate of oxygen consumption in 5-day experiments, but no marked deviation from the normal occurred when this preparation was given for from 10 to 20 days. The feeding of various amounts of desiccated

thyroid substance or the administration of thyroxin to immature rats injected with acid gonad-stimulating extracts made from either sheep anterior hypophyses or human pregnancy blood, resulted in a markedly lessened increase of uterine and ovarian weight. There were no demonstrable histological differences between the ovaries of the control and thyroid-fed animals given the sheep anterior lobe extract. In some instances the injection of the extract made from blood of pregnant women to immature thyroid-fed rats resulted in an extensive production of interstitial tissue in the ovaries. The administration of a gonad-stimulating and thyroid-stimulating extract made from anterior pituitary glands of sheep to immature rats produced greater increases of ovarian weight when a partial or complete thyroidectomy had been first performed. This is considered as further evidence that the over-active thyroid inhibits ovarian function. The injection of a gonad-stimulating extract prepared from blood of pregnant women to immature rats did not produce a greater increase of ovarian weight when a partial or complete thyroidectomy had been first performed.—Author's Abst.

The action of thyroxine on the milk and milk fat production of cows. Graham, W. R., Jr., Biochem. J. **38:** 1368. 1934.

Five normal cows, past the peak of their lactation cycle, were treated with synthetic thyroxine, desiccated thyroid glands, 2-4 dinitrophenol or prolactin during the course of the experiment. The animals all responded to injections of thyroxine or thyroid feeding by an increase in milk fat production. The increase in milk secretion following this treatment was more variable than that of fat production but always showed at least a slight upward trend. The results following the feeding of dinitrophenol or injections of prolactin were inconclusive.—Author's Abst.

Histologic changes in the thyroid gland of the rabbit following injection of urine. Hellwig, C. A., Arch. Path. **15:** 321. 1933. Abst., Am. J. Obst. & Gynec. **28:** 622.

Friedman recommended the use of female rabbits instead of mice for the biologic pregnancy test. Krjlow and Sternberg reported structural changes in the thyroid gland of the female rabbit following copulation. These changes were characterized by marked enlargement and hyperemia, disappearance of the colloid and increased height of acinar epithelium. In the light of this knowledge, the thyroid glands in those animals showing positive Aschheim-Zondek reactions might also show changes similar to those found following copulation. If this were true, an additional positive sign of pregnancy might be found by examining the thyroid gland of the rabbit after injection of urine. Hellwig made such a study. Sixty-four thyroid glands were obtained from animals used for the biologic pregnancy reaction. Hyperplasia of the thyroid gland occurred in rabbits irrespective of the results of the Aschheim-Zondek test. The assumption seems justified that the active substance in the urine is identical with the thyrotropic hormone of the anterior lobe of the hypophysis although different from the active substance present in the urine of pregnant women, viz., prolan which stimulates the ovaries. Injection of urine into rabbits presents an easy, rapid and almost certain method for studying the histogenesis of thyroid hyperplasia.

The correlation of mineral metabolism and the vegetative nervous system in thyroid disease. Klein. J., Ann. Int. Med. **8:** 798. 1935.

Observations are reported on 44 animals divided into four groups. Seven animals received normal diet, 14 an iodine-free diet consisting of pearl barley and distilled water, 13 others received the same diet but were daily treated with subcutaneous injections of adrenaline, two minims (1-1000) each, while 10 received the same treatment together with 3% calcium lactate in the drinking water. The thyroid glands were fixed and studied microscopically. The follicular diameter was measured with an ocular micrometer and the average of a large number of measurements taken. It was found that deficiency of iodine in the diet caused atrophy of the thyroid follicles and loss of colloid. The injection of adrenaline in animals suffering iodine deficiency caused hyperactivity of the thyroid epithelium with increased secretion of colloid, hyperplasia, hyperemia and hyperplastic changes. Addition of calcium to the regimen promoted colloid storage and neutralized the harmful effect of the sympathetic stimulation.—R. G. H.

Correlation between the clinical and the histological picture of goiter (Die Korrelation zwischen dem klinischen und dem histologischen Bild der Struma). Lanz, O., Nederl. tijdschr. v. geneesk. P. 588. 1933. Abst., Endokrinologie, **12**: 384.

There is a marked difference between the type of goiter prevalent in Switzerland and in Holland in that the former represents the type struma nodosa and the latter struma diffusa. The Dutch forms show more often symptoms of hyperthyroidism, the Swiss, hypothyroidism. The diffuse form shows three different types: soft, follicular hyperplasia; parenchymatous type; and diffuse colloidal type. In all these types iodine is the best treatment. In the case of struma nodosa iodine is harmful, as it might lead to toxic goiter. The most important problem is whether the goiter is toxic or non-toxic. The latter ones are treated the same way as in Switzerland; the toxic ones, after short, internal medication, are treated surgically. The only correct classification of goiter is the etiologic-pathogenetic.—G. L. Banay.

Maintenance requirement of myxedema patients; clinical and chemical assay of commercial thyroid preparations. Lerman, J. and W. T. Salter, J. Pharmacol. & Exper. Therap. **50**: 298. 1934.

Six lots of thyroid gland tablets obtained from 4 different companies (Armour; Lederle; Burroughs, Wellcome; and Parke, Davis) were analyzed for total organic iodine and thyroxin iodine. Each lot was given to a patient for a period of 2-3 months, and the maintenance level of metabolism determined. Twenty patients with myxedema were thus tested, some receiving two lots, others more. The results indicate that the calorigenic action of whole thyroid is determined by its total organic iodine rather than its thyroxin iodine content. There is considerable discrepancy in the strength of the various commercial thyroid preparations, both in iodine content and in calorigenic activity. In terms of dosage by weight, the following are roughly equivalent calorigenically: Armour's thyroid (desiccated), 1.5 grains; Lederle's thyroid (desiccated), 1.5 grains; Burroughs, Wellcome's thyroid (fresh gland), 5.0 grains, and Parke, Davis' thyroid (dessicated), 1.0 grain.—J. Lerman.

Action of iodine in thyrotoxicosis, with especial reference to refractoriness. Means, J. H. and J. Lerman, J. A .M. A. **104**: 969. 1935. Abst., A. M. A.

The authors point out that the clinical facts regarding iodine in thyrotoxicosis are that it produces an altogether characteristic and specific response, which consists in an amelioration of symptoms and a drop in metabolic rate. This response will occur at any stage of the disease. It appears that the response has no relation to the duration or direction of progress of the disease but merely acts as a check on the intensity of its symptoms. These clinical facts are consistent with the theory that in thyrotoxicosis the thyroid allows the escape of thyroxine to proceed at an excessive rate; to leak, in fact, and that the cells of the thyroid hyperfunction in consequence. Iodine, it is suggested, sets up a temporary obstacle to this excessive outflow: it checks the leakage of thyroxine from the gland. The known facts of iodine and thyroxine content of the gland, blood and urine are consistent with such a theory. The authors believe that so-called refractoriness is apparent, not real. Thyrotoxic patients who are unaffected by iodine are those who are already fully iodinized. They doubt the existence of so-called iod-Basedow. The iodine response is valuable in the management of toxic goiter, both in treatment and in diagnosis, but its fundamental nature must be familiar if it is to be used successfully.

Keratoderma of the soles of the feet and palms of the hands in a case of hypothyroidism cured by thyroid extract (Kératodermie plantaire et palmaire chez une hypothyroïdienne. Sa guérison par la thyroïdine). Mussio-Fournier, J. C., Bull. et mém. Soc. méd. d. hôp. de Paris, **48**: 1236. 1932.

A woman of 60 presented a picture of thyroid insufficiency manifested by swelling of the face, dry skin, reduced transpiration, scanty hair, extreme sensitivity to cold, edema of the extremities, diminution of thirst, and constipation. On the other hand, there were no psychic troubles or slowness in walking, speech or movements which are usually seen in the myxedemic type. The basal metabolic rate was not determined. The blood Wassermann gave negative findings and the urine examination revealed only 10 cgm. of albumin per liter. There were no other pathological findings except the marked keratoderma of the soles of the feet and the palms of the hands. Thyroid treatment was insti-

tuted—20 cgm. per day. After about four weeks of treatment the symptoms of thyroid insufficiency disappeared and the keratosis was completely cured in about five months.—M. O. L.

Preventive treatment of goiter in schools. Quigley, J. M., Pennsylvania M. J. **38**: 185. 1934.

For several years Quigley and his associates have employed chocolate tablets each carrying one-sixth of a grain of iodine, in the prevention of goiter in school children at Clearfield, Pa. No untoward effects from this form of treatment have been observed. The tablet is given once a week during the entire school term of 40 weeks.—I. B.

Hyperthyroidism treated by irradiation. Quiney, J. J., Pennsylvania M. J. **38**: 480. 1935.

Except in those patients who are extremely toxic and those suffering from pressure effects produced by the enlarged gland, Quiney believes that there are no contraindications to the use of roentgen rays or radium in the treatment of hyperthyroidism. He presents a report of 73 cases of hyperthyroidism seen in private practice and treated by roentgen rays. It shows recovery in 89.7% of the cases in which treatment was completed, improvement in 8.1%, and no improvement in 2.4% of the cases. It indicates the value of the basal metabolic rate, the weight, and the pulse rate as guides to improvement or lack of improvement. From the foregoing it is evident that hyperthyroid subjects, with few exceptions, should receive roentgen-ray treatment. The comparatively few not cured by roentgen-ray treatment may then submit to surgical treatment, which does not offer better results, if as good, but is effective in some cases in which response to irradiation therapy is not satisfactory.—I. B.

The rôle of the hypophysis in thyroid syndromes. Rony, H. R., Illinois M. J. **66**: 234. 1934.

The author points out that it is necessary to differentiate between primary and secondary thyroid disturbance. The latter is defined as due to abnormal supply of the anterior lobe thyrotropic hormone. The possibility of such differentiation and its difficulties are illustrated by cases of hypothyroidism and hyperthyroidism observed by the author, and the practical importance of this differential diagnosis is discussed.—I. B.

The effect of diiodotyrosine on the basal metabolism in myxedema. Thompson, W. O., J. M. Alper, Phebe K. Thompson and L. F. N. Dickie, J. Clin. Investigation, **13**: 29. 1934. Abst., Chem. Absts. **29**: 1767.

The intravenous administration of diiodotyrosine was without effect on the basal metabolism of patients with myxedema. This compound is not the limiting factor in thyroxine formation in individuals with very small amounts of active thyroid tissue nor can it be synthesized to thyroxine outside the thyroid.

The pharmacology of the thyroid in man. Thompson, W. O., Phebe K. Thompson, S. G. Taylor III, S. B. Nadler and L. F. N. Dickie, J. A. M. A. **104**: 972. 1935. Abst., A. M. A.

The authors observe that in a normal man the thyroid forms thyroxine or its equivalent at the rate of about 0.3 mg. a day and that there are about from 10 to 14 mg. in the body outside of the thyroid. Following the intravenous administration of a single dose of 10 mg. of thyroxine to a patient with myxedema, there is a marked lag in the clinical improvement behind changes in the metabolic rate, the period of highest metabolism being characterized by intoxication and the period of falling metabolism by improvement. Observations on the calorigenic action of diiodotyrosine, thyronine, diiodothyronine and N-acetyl thyroxine show that the amino group, the diphenyl ether group and all four iodine atoms are essential for the maximal effect of thyroxine. The increase in metabolism produced by dinitrophenol in myxedema, with little or no clinical improvement, suggests that there may be different types of altered metabolism that cannot be differentiated by changes in the rate of oxidation alone. As the complexity of the molecule of various thyroxine compounds increases, the greater will be their absorption from the gastro-intestinal tract and hence the

less the effect of alkali in augmenting the absorption. As a result of digestion with pepsin, data have been obtained which suggest that nearly all the calorigenic activity of the whole gland is possessed by less than half of the total iodine (acid-insuluble precipitate). The acid-soluble portion does possess slight calorigenic activity and after a single large dose the metabolism appears to return to its level before treatment more rapidly than after an equal change produced by the acid-insoluble precipitate. After heating with approximately normal sodium hydroxide for four hours, desiccated thyroid loses more than two-thirds of its calorigenic activity, whereas thyroxine is unaffected by the same treatment. The subcutaneous administration of extracts of the anterior lobe of the pituitary produced an increase in basal metabolism in 18 of 28 patients of various types, including 2 with hypopituitarism, 10 with low basal metabolism of unknown cause, several with nontoxic goiters, including 3 patients with mild myxedema and 1 case of exophthalmic goiter. During the injections in the patient with exophthalmic goiter, a mild case of the disease became a moderately severe one.

Stimulation of mammary gland development in the pregnant rat under conditions of experimental hyperthyroidism. Weichert, C. K. and R. W. Boyd, Anat. Rec. **59**: 157. 1934.

The mammary glands were removed from a series of pregnant rats made hyperthyroid by feeding 0.5 gm. of desiccated thyroid gland daily, beginning with the first day of pregnancy. These glands were compared with the mammary glands of normal pregnant rats at corresponding time intervals. A total of 23 rats was used in the experiment and in each of these animals only the next to the last pair of mammary glands was removed for study. The series of glands removed from the hyperthyroid animals showed an appreciable stimulation even on the fifth day of pregnancy. Between the seventh and ninth days a very marked increase in glandular development took place in comparison with normal controls. From this time until the end of pregnancy the thyroid-fed animals showed a great difference in the amount of mammary tissue and in the earlier appearance of secretion in the alveoli. It is suggested that the heightened metabolic rate resulting from the hyperthyroid condition may perhaps reduce the normal oestrin level, removing, to some extent, its inhibitory action on the hypophysis. That organ may thus elaborate its hormones to an increased extent. The hypophyseal and corpus luteum hormones being present in relatively greater concentration than in the normal animal may therefore cause the mammary gland to develop with exceptional rapidity.

—C. K. Weichert.